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Effectiveness And Cost Effectiveness Of Cognitive Behaviour Therapy And Short-Term Psychoanalytic Psychotherapy Compared With Brief Psychosocial Intervention In The Maintenance Of Symptomatic Remission In Adolescents with Unipolar Major Depression (IMPACT): A Randomised Controlled Trial

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Competing Interests

All authors declare no competing interests.

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List of abbreviations

Glossary of terms

BPI-S - Brief Psychosocial Intervention Scale

CAMHS - Child and Adolescent Mental Health Services

CPPS - Clinical Psychotherapy Process Scale

DES-Q – Depressive Experiences Questionnaire

EQ-5D – ~~Quality of Life Questionnaire~~EuroQol measure of health-related quality of life

LME – Linear Mixed Model

ICC – Intra-class Correlation Coefficient; also Intra-cluster Correlation Coefficient

SSRI- Selective Serotonin Reuptake Inhibtors

BPI – Brief Psychosocial Intervention

CBT – Cognitive Behaviour Therapy

STPP- Short Term Psychoanalytic Psychotherapy

K-SADS-PL - Kiddie-Schedule for Affective Disorders and Schizophrenia

CA-SUS - Child and Adolescent Service Use Schedule

MFQ - Mood and Feelings Questionnaire

MDD - Major Depressive Disorder

RCMAS - Revised Children's Manifest Anxiety Scale

LOI - Leyton Obsessional Inventory

APQ - Antisocial Personality Questionnaire

HoNOSCA - Health of the Nation Outcome Scales

RTSHIA - Risk Taking and Self Harm Inventory - Adolescent version

Plain English Summary

Clinical depressions emerge in the adolescents. Whether treatment for the acute episode is able to reduce and maintain non-clinical levels of depressive symptoms up to 18 months after psychological therapy began is not known. This study evaluated whether the clinical and cost effectiveness of receiving a longer term more intensive treatment with a specialist trained therapist was more beneficial than a brief, practise based treatment given by a psychiatrist or other mental health professional working in routine specialist Child and Adolescent Mental Health Services (CAMHS) in England. By18 months there was no significant difference between the treatment groups in the mean depressive symptoms score, the total treatment costs or quality of life. The study demonstrates that all 3 psychological treatments are as clinically and cost effective as each other in maintaining reduced depressive symptoms.

Scientific Abstract

We tested whether, compared to a short term brief psychosocial intervention (BPI; a manualised problem focussed psychoeducation package), two more intensive, longer term and more theory based psychological treatments, short term psychoanalytic therapy (STPP) or cognitive behaviour therapy (CBT), were associated with the maintenance of lower depressive symptoms 18 months after treatment began. A pragmatic superiority RCT was conducted on depressed adolescents (11-17 years at entry) meeting criteria for unipolar major depression episode. The duration of the trial was 86 weeks. A 36 week treatment phase preceded a follow up assessment period reassessing patients at 52 and 86 weeks post randomisation. The primary clinical outcome measure was self-reported depressive symptoms occurring in the past 2 weeks. The study included 470 patients who were randomly assigned to BPI (n=158), CBT (n=155) and STPP (n=157) respectively. Clear treatment adherence and differentiation were established between the three interventions. There was no statistically significant difference in depression symptom scores between the three treatments over the follow up period (36-86 weeks: treatment effect 0.41, 95% CI, -2.901 to 3.723, p= 0.81). There were no differences in total costs or quality of life scores between treatment group. Prescribing of an SSRI before or during the trial was no different between the treatment groups and did not influence the results. For major depression in adolescents referred to CAMHS any of the 3 psychological treatments investigated in this study can be prescribed as they are equally as likely as each other to maintain reduced depressive symptoms and improve quality of life in the medium term. Clinical planning of 6-8 sessions in the first instance may be advisable. This could reduce costs associated with booked bit not attended treatment sessions and be no less effective than longer planned treatment.

Executive Summary

Background

Unipolar major depressive disorder (MDD) emerges in the adolescent years as episodes of mental illness and is associated with a high risk of symptomatic and episode recurrence into adult life. Whether treatment for the acute episode is able to reduce and maintain non-clinical levels of depressive symptoms up to 18 months after psychological therapy began is not known.

Objectives

We aimed to test whether, compared to a short term brief psychosocial intervention (BPI; a manualised problem focussed psychoeducation package), two more intensive, longer term and more theory based longer term psychological treatments, short term psychoanalytic therapy (STPP) or cognitive behaviour therapy (CBT) were associated with the maintenance of lower depressive symptoms 18 months after treatment began.

The objectives of this study were to evaluate whether the clinical and cost effectiveness of receiving a theory based longer term more intensive treatment with a specialist trained therapist was more beneficial than a brief, practise based treatment given by a psychiatrist or other mental health professional working in routine specialist Child and Adolescent Mental Health Services (CAMHS) in England.

The specific research hypothesis addressed was that compared with a brief psychosocial intervention (BPI) receiving either of the specialist intensive psychological treatments (STPP or CBT) would:

- Result in lower self-reported depressive symptoms at follow up assessments completed at 52 and 86 weeks after treatment began.
- Be as cost effective as BPI.
- Result in fewer patients meeting diagnostic criteria at final evaluation.

Design

A pragmatic superiority RCT was conducted on depressed adolescents (11-17 years at entry) meeting criteria for unipolar major depression episode.

Setting

Participants were recruited from 16 NHS Child and Adolescent Mental Health Services (CAMHS) clinics from three centres in England: East Anglia, North London and North West England.

Interventions

Participants were randomised to one of three active psychological treatment arms: Brief Psychosocial Intervention (BPI), Short Term Psychoanalytic Psychotherapy (STPP) or Cognitive Behaviour Therapy (CBT). Over the course of the study patients were allowed to receive an Serotonin Specific Re-Uptake Inhibitor (SSRI) in addition to psychological treatment if they met National Institute of Clinical Excellence guidelines for combined treatment to aid clinical remission by end of treatment. Psychological treatment adherence and differentiation were rated using the Comparative Psychotherapy Process Scale (CPSS).

Outcome measures

The duration of the trial was 86 weeks. A 36 week treatment phase preceded a follow up assessment period reassessing patients at 52 and 86 weeks post randomisation. The primary outcome measure was self-reported depressive symptoms occurring in the past 2 weeks. Secondary outcome measures were: self-reported anxiety, obsessive and antisocial symptoms; personal and social function function (Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA); and interviewer-rated clinical diagnosis. Cost effectiveness was evaluated using the Child and Adolescent Service users Schedule (CA-SUS).

Results

Between June 29th 2010 and January 17th 2013 we assessed 557 patients of whom 87 were excluded as not meeting eligibility criteria and 470 were included. These were randomly assigned to BPI (n=158), CBT (n=155) and STPP (n=157) respectively. Clear treatment adherence and differentiation were established between the three interventions. There was no statistically significant difference in depression symptom scores between the three treatments over the follow up period (36-86 weeks: treatment effect 0.41, 95% CI, -2.901 to 3.723, p= 0.81). At 86 weeks there was no significant difference in the mean depressive symptoms score between treatment groups nor in the proportion of patients meeting diagnostic criteria for major unipolar depression episode. There were no differences in total costs or quality of

life scores between treatment group. Prescribing of an SSRI before or during the trial was no different between the treatment groups and did not influence the results.

Conclusions

For major depression in adolescents referred to CAMHS any of the 3 psychological treatments investigated in this study can be prescribed as they are equally as likely as each other to maintain reduced depressive symptoms and improve quality of life in the medium term. Clinical planning of 6-8 sessions in the first instance may be advisable. This could reduce costs of non attendance and be no less effective than longer planned treatment.

Recommendations for future research

- **Determine the characteristics of depression prior to intervention that index the risk for non-response to treatment**

Delineating the antecedent factors that can identify treatment non response is a key study to prevent application of non therapeutic methods and to aid the development of new tretaments for those likely to show persistent depression.

- **A study to investigate treatment for cases resistant to first line therapies**

Designing and implementing an intervention study for treatment resistant depressed adolescents to reduce adult service use and personal morbidity is a high priority.

- **Mechanisms of treatment response**

The results suggest a potentially common neurocognitive basis for treatment response and maintenance of reduced depressive symptoms. Revealing mechanisms that subserve treatment response should be a focus for further investigation using experimental medicine methods. Such approaches could identify an antecedent endophenotype for treatment success.

- **Person Centred Treatment Research**

The comparable outcomes for different treatment modalities suggests a more person centred approach to determine what treatment will work best for what patient is a priority for future

research. Revealing common therapeutic and more specific treatment factors using quantitative and qualitative person centred analyses are called for.

- **Implementation in non specialist settings and by less specialist staff**

The findings relate to the specific environment of a specialist CAMHS clinic and relatively severely depressed adolescents. Whether any of these three therapies can be delivered with equal clinical and cost effectiveness by less highly-qualified practitioners in non speciliast settings is an urgent research question.

Chapter 1

Introduction

Unipolar major depression (MD) in adolescents

Unipolar major depression (MD) is a significant mental illness affecting a substantial proportion of the adolescent population worldwide (1). The disorder presents in episodes and the estimated 12 month period prevalence of MD episodes in teenagers is 7.5% affecting around twice as many girls as boys with an estimated 1 in 4 of these experiencing a severe, impairing and clinically referable condition (2, 3). There is a growing concern based on longitudinal evidence that the consequences of some adolescent emergent MD episodes include suicide, persistent and chronic mental health disorders, substance misuse and failure to achieve both educationally and in the work place (4). Furthermore in adults there is evidence that a history of depression may interfere with treatment compliance and self care in patients with type 2 diabetes and cardiovascular disease (5). These latter correlates suggest that reducing incident risk for depression early in life may have wider physical health care benefits for later in the life course. These medium and long-term negative outcomes also come at great economic cost to the UK and other nations, including in the developing world where depression has been noted to be at least as disabling as any other chronic illness in adult life as urbanisation increases (6, 7). Therefore clinical methods for the treatment of depressed adolescents must go beyond short-term remission of a single episode to include amongst its objectives reducing the risks for diagnostic relapse and recurrence risk by lowering depressive symptoms before independent adult life.

The combined effect of high level of emerging mental illness with long term consequences for health, together with the increasing demands for treatment from adolescents and their parent, makes it imperative to provide effective interventions that can be implemented by developing the current mental health workforce (8, 9). From this policy perspective it is also essential to consider the extent to which any effective treatment is deliverable and affordable. Currently, the cost-effectiveness of treatments aimed at reducing recurrence risk by lowering

depressive symptom rate and avoiding diagnostic relapse up to 18 months after entering treatment, are not known.

Are there effective treatments for depressed adolescents?

Over the past 20 years there have been a series of important randomised controlled trials determining both the efficacy and clinical effectiveness of psychological and pharmacological treatments for depression in adolescents that result in remission in the short term i.e. by 28 weeks (10, 11). Original guidance compiled in 2005 by the National Institute for Health and Care Excellence (NICE) for the treatment of a moderate to severe depression episode, referred to and treated in NHS CAMHS, advised the use of evidence-based psychological therapies, such as cognitive behaviour therapy, as the first line treatment, with selective serotonin reuptake inhibitor (SSRIs) antidepressants constituting the pharmacological treatment of choice only if there was no satisfactory response (12). The 2015 revisions now recommend that as a first line treatment for a major depression episode, defined as >5 symptoms and associated with observable personal impairment, an SSRI may be used in combination with psychological therapy (individual CBT, interpersonal therapy, family therapy, or psychodynamic psychotherapy) that runs for at least 3 months as a first line treatment (13). The revised 2015 guidelines continue however to warn against the use of SSRIs on their own. Furthermore, this revision applies only to patients with moderate to severe depressions, defined as 5 or more symptoms associated with concurrent impairments in personal, social or educational life domains for longer than two weeks.

Research studies in adults have provided evidence for the clinical effectiveness of a number of psychological therapies for inducing clinical remission for adult patients suffering with a moderate to severe depression episode. These include cognitive behaviour therapy (14), interpersonal therapy, short term psychoanalytic therapy (15) and non-directive brief psychosocial interventions (16). Overall psychological therapies appear effective in a broadly equivalent manner although results vary with methods and measures (17). Current evidence indicates however that findings from adult patients cannot be assumed to reflect comparable efficacy or effectiveness for depressed adolescents (18).

Evidence from RCTs with adolescents to date suggests that CBT is not rapidly therapeutic in the acute phase of treatment (10). Furthermore, in the short term, CBT may not provide added

clinical value when patients are already receiving fluoxetine plus active specialist clinical care in a UK CAMHS setting (11). There is relatively little evidence on the use of Short-term Psychoanalytic Psychotherapy (STPP) with children or adolescents, although the one clinical trial with this population had encouraging outcomes (19).

Interpersonal psychotherapy is effective with adolescents (IPT-A) with mild to moderate depression in the short term but no evidence for efficacy in patients with a moderate to severe depression episode exists. Relatively brief, problem-solving approaches with a focus on promoting good interpersonal relationships may be of value in more severe forms of this illnesses but this remains to be fully evaluated (20, 21). However, IPT-A is not widely available on the NHS in the UK to treat depression in adolescents although this problem is being addressed as part of the Improved Access to Psychological Therapies initiative of NHS England (22).

Brief psychosocial intervention (BPI) incorporates general principles from psychological therapies (e.g. agenda setting, problem solving, and facilitating relationships with peers, school and family). BPI has recently been formalised into a manual for systematic delivery within CAMHS clinics for the treatment of MD aimed at inducing short term remission (23). A previous RCT reported that BPI combined with fluoxetine is as effective as BPI combined with fluoxetine and CBT in producing remission at 28 weeks of treatment (11). It is not known if BPI alone is efficacious and clinically effective in the short term for patients suffering from a moderate to severe depression episode.

Only one study has tested the efficacy of any treatment against no treatment and showed that time to remission is significantly quicker for SSRIs and SSRIs+ CBT against pill placebo (10). In contrast, all recent RCT studies to date have focussed on establishing clinical effectiveness in reducing immediate symptoms and restoring personal functioning (10, 11, 24). Whilst there is evidence for clinical effects, there is no evidence that any of the aforementioned treatments, individually or in combination, is efficacious in reducing recurrence risk by lowering depressive symptom rate or diminishing diagnostic relapse in the medium term i.e., a year or more following intervention.

This lack of understanding about therapeutic effects on recurrence risk and clinical relapse is compounded by a remaining concern regarding the extent of the effectiveness of existing

treatments and the natural history of these disorders (3, 4, 25). RCT data to date has shown that, even where treatment is successfully delivered, a substantial number of depressed adolescents do not recover or relapse following recovery. Thus the proportion of depressed patients who meet criteria for clinical remission does not rise above 70% by 28 weeks from the start of treatment. Indeed in studies of moderate to severely ill depressed adolescents, one RCT in the UK clinical outcome assessment reported only 42% were very much or much improved by 12 weeks rising to 53%-61% by 28 weeks (26). Of the remaining patients, a further 30% described themselves as no better or worse at 12 weeks falling to 18%-24% by 28 weeks (26). A recent meta-analysis noted that, compared to CBT alone, the combination of fluoxetine and CBT may produce greater improvement in psychosocial functions but no greater reduction in residual symptoms (27). Even for successfully treated cases there is a high relapse rate in the next 5-10 years. Overall some 50%-70% of patients attending an NHS clinic may relapse in the 10 years between mid-adolescence and young adulthood, coinciding with some of the largest educational milestones and social changes they may face over their lifetime (3, 4, 25).

To date there had been two naturalistic follow up investigations of psychological treatment effects in the medium term (i.e. >52 weeks) in depressed adolescents entered into randomised trials. Both these studies show that the likelihood of recurrence and relapse of diagnosis following successful treatment is substantial occurring in 50%-75% of treated patients, beginning within 1 year of clinical remission and being significantly higher in patients with recurrent versus single episodes (28-30). These studies were less than 150 patients each and did not plan to investigate the relative effects of treatment in maintaining reduced depressive symptoms in the medium term.

There are no studies in the NHS that have investigated clinical effectiveness of specialist or general psychological treatments in reducing symptomatic recurrence risk or diminishing clinical diagnostic relapse in the medium term up to 18 months following accessing treatment. Therefore, it is unclear if there are superiority effects of one psychological treatment over another in reducing and maintaining lower depressive symptoms over time and therefore diminishing symptomatic recurrence risk.

Theoretically, psychodynamic practitioners suggest that potentially more enduring changes will be associated with this form of psychological treatment, as it aims to address and repair abnormal underlying mental models of interpersonal relationships. In a similar way,

cognitive-behaviour therapists theoretically aim to teach new more adaptive methods of behaving and thinking, which should be continues after therapy ends and thus reduce long-term relapse of disorder. These forms of therapy are therefore hypothesised to be more likely , if successful, to predict more enduring recovery when compared with therapies simply addressing current symptom reduction, alleviating the impact of provoking life events and difficulties, providing psychoeducation and problem solving advice.

Rationale for the current study

The current study was devised knowing that there is now a clear evidence base for implementing psychological treatments that are clinically effective for inducing short term remission but whose efficacy for: i) reducing recurrence risk indexed by rising depressive symptoms in the medium term 18 months after treatment began or ii) preventing clinical diagnostic relapse after treatment is completed, remains unknown. The literature implicates a number of candidate specialist psychological treatments for putative effects on reducing recurrence risk and relapse rates, among which are CBT and STPP. Both treatments aim to reduce symptoms and future risk of relapse. Given clear-cut evidence that in depressed adolescents active psychological treatments are clinically more effective than no treatment, a pragmatic effectiveness superiority trial was conceived as the best design. The standard treatment chosen as the reference therapy was BPI, a relatively brief (i.e. max 12 sessions) psychosocial approach to problem solving, mental hygiene and well-being management with education about depressive illnesses. BPI is, by definition, shorter than specialist psychological therapies and is aimed theoretically at gaining remission as quickly as possible form the depression episode. The therapeutic protocol therefore focuses on practical advice giving, psychoeducation about depression and how to manage daily life challenges.

Therefore we designed an RCT to test the risk reduction effect of two specialist psychological treatments against a briefer treatment primarily focussed on short term clinical remission. In each of the 3 arms of the RCT, SSRIs were available as a combination treatment option following the 2005 NICE guidelines.

The study must allow for the prescribing of SSRIs as short term clinical effectiveness is also achievable with fluoxetine without the addition of a protocol driven psychological therapy (10). As with psychological treatments, however, the contribution of SSRIs to reduce

recurrence risk and relapse rate remains unknown. There is also evidence that cases which have been resistant to other antidepressant medication may show significant clinical improvement with a change to a different SSRI, if prescribed in conjunction with CBT (24). This is the only published study of treatment resistance in depressed adolescents and suggests that medium term treatment goals may be best achieved by combination therapies. This remains to be evaluated in a systematic RCT where reduction in recurrence risk and relapse rates is the clinical outcome objective. Nevertheless in the current study we judged it essential to abide by current NICE guidelines for the NHS and allow SSRI prescribing within each arm based on clinical judgment of psychological treatment progress.

Given the importance of cost-effectiveness and deliverability within the NHS, we also included an economic evaluation component to the trial. Results from a previous RCT conducted in the USA suggest that CBT alone is relatively expensive and cost-ineffective compared to an SSRI alone. The same RCT demonstrated that fluoxetine alone was much more cost-effective than combined fluoxetine-CBT over 12 weeks (31). In the UK, a RCT reported that adding CBT to an existing combination treatment of fluoxetine plus active specialist clinical care (the non-manualised forerunner of BPI) in a CAMHS setting was not cost-effective over 28 weeks (32). Whether more expensive psychological treatments may become cost-effective in the medium term, by diminishing the subsequent use of health, education and social services more than a 'treatment as usual' or BPI protocol, is not yet known.

For this study only clinic-referred depressed adolescents deemed in scope for recruitment included those with suicidal thoughts, psychotic behaviours and non-depression comorbid disorders. This is comparable to the ADAPT study but distinguishes both of these UK studies from the major study of adolescent depression (TADS) in the USA, as suicidal and psychotic presenting cases were excluded from TADS, and participants were recruited by advertisement (10, 26, 33). Participants were recruited from patients referred to routine NHS clinics. All trial participants were treated in standard clinical settings using NHS staff to deliver treatments under supervision. This maximised ecological validity and generalisability to NHS settings and was intended to assure commissioners and providers that the study results could inform routine NHS service design, delivery and implementation.

Unlike the UK ADAPT RCT (11), cases who responded to an initial phase of brief psychosocial intervention (2-3 weeks), and who therefore may have been close to remission or especially responsive, were not excluded. This is because this study is concerned with, and has a primary hypothesis for, recurrence risk defined by a 5 point increase in self-reported depressive symptoms over the repeated assessment time up to 18 months after first assessment prior to treatment allocation and activation. Also unlike prior UK RCT studies (11, 34), we added potential moderators of recurrence risk and relapse rates. These were individual differences in: i) self-reported rumination (persistently brooding or dwelling, often to the exclusion of other themes in the patient's life) (35, 36) and ii) depressive thinking style (the extent to which patients with clinical depression may be characterized in terms of immaturity of the cognitive styles of self-criticism and perfectionism) (37-39).

Aims and objectives

This superiority powered pragmatic effectiveness randomised controlled trial was designed to determine i) whether psychological treatment delivered to adolescents with unipolar major depression would reduce risk of recurrence thought lowering depressive symptoms by 86 weeks post randomisation. As this was designed as a superiority effects trial we tested whether, compared to a standard brief psychosocial intervention, 2 specialist psychological treatments were more likely to result in lowering the rate of depressive symptoms from randomization to 86 weeks after beginning treatment.

The primary objective contained 2 related questions. First and was to determine whether in a specialist CAMHS setting, Cognitive Behaviour Therapy (CBT) and Short Term Psychoanalytic Psychotherapy (STPP), were superior in reducing self-reported depressive symptoms over time compared to a standardised Brief Psychosocial Intervention (BPI). The second was to test if there were superiority effects of STPP over CBT for lowering depressive symptoms by 86 weeks. An additional but secondary objective was to evaluate whether these specialist individual psychological treatments were more effective than standard BPI at reducing clinical diagnostic rate for major depression episode by 18 months after randomisation. The study was not however powered to consider this diagnostic investigation as primary hypothesis.

Specific hypotheses

This RCT tested a primary superiority clinical effectiveness hypothesis that compared to the reference BPI treatment :

- STPP and CBT are both independently more clinically effective at maintaining a reduction in depressive symptoms at 52 and 86 weeks reassessment after randomisation.

The secondary hypothesis tested was that:

- STPP is superior in maintaining a reduction in depressive symptoms over the follow up assessments (52 and 86 weeks) when compared to CBT.

The RCT also tested an economic hypothesis to determine:

- Whether any additional costs of specialised treatments accrued by end of treatment are justified by decreased use of resources (health, education and social care services, voluntary agencies) by 86 weeks follow up.

Chapter 2

Methods

The procedure for the study was to ascertain and recruit patients with an episode of DSM-IV major depression from routine NHS specialist CAMHS in 3 parts of the UK: East Anglia, North London and the North West of England (Manchester and the Wirral).

East Anglia is a largely rural area of 3 million people, with 4 cities each containing approximately 100,000 people; North London is a densely populated urban sector of the metropolitan London region with around 4 million people; North West England is a region covering approximately 4 million people of whom about 1 million are living in rural surroundings, with a further 3 million residing in the northern and central sectors of the large metropolitan area of the City of Manchester. Participants were recruited from 18 [we said 16 earlier?] routine CAMHS clinics who agreed to participate from within these three regions.

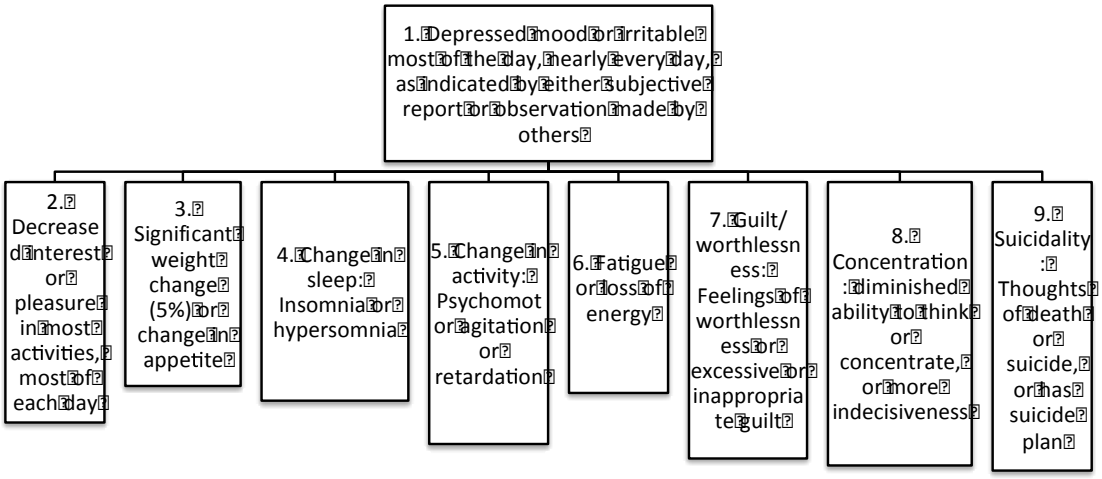
The RCT was approved and monitored by the Multi-Centre Research Ethics Committee in Cambridgeshire. The sponsors were Cambridge and Peterborough NHS Foundation Trust, Cambridgeshire; Camden and Islington NHS Foundation Trust, North London; Cheshire and Wirral Partnership NHS Foundation Trust and the Central Manchester University Hospital NHS Foundation Trust. A scientific steering committee met 6 monthly over the course of the RCT (Chair: Professor Philip Cowen, University of Oxford, Professor Paul Stallard, University of Bath, Professor David Brent, University of Pittsburgh, Professor Sabine Landau, Kings College, London) and a data management committee which also met 6 monthly (Chair: Professor Rona Campbell, University of Bristol, members: Dr Nicola Wiles, University of Bristol, Professor Anna Marie Albano, Columbia University). The NHS Coordinating Centre for Health Technology Assessment audited accrual, progress and quality of the study throughout.

The research teams in each of the 3 regions contacted their regional clinics on a weekly basis to ascertain if there were any patients referred. The first point of contact was with clinical NHS staff who determined if their patient was in scope for the RCT. An initial screening checklist for major depression episode was provided to the clinics by the research team and used to inform the research assessors of potential cases aided this clinical task.

Recruitment

Participants were recruited if they met criteria for an episode of DSM-IV major depression and were aged between 11 and 17 years. This diagnosis is achieved by the presence of at least 5 symptoms, one of which must be a mood symptom present nearly everyday and most of the day for at least 2 weeks, together with 4 others, and accompanied by observable personal and/or social impairment. The criteria are shown in Figure 1.

Figure 1: DSM IV criteria for Major Depression Disorder



Mood change plus 4 other symptoms required for the diagnosis.

Participants were recruited as follows: clinical staff who considered a patient was depressed completed the research checklist and asked them and their parent or guardian if they would consider taking part in an RCT investigating the extent to which treatment was able to lower recurrence risk and relapse rate. They were informed that the trial only included and compared

treatments already known to contribute to producing clinical remission. If they expressed interest in the study their contact details were passed to the research group; research staff contacted the patient with an expression of interest letter and a replay paid envelope.

Inclusion criteria

- Age 11 through 17 years
- Current diagnostic episode of DSM-IV unipolar MDD.

Patients with suicidal intent past or recent suicidal behaviour, psychotic symptoms or any comorbidity, other than those specifically defined in the exclusion criteria below, were included.

Patients who met inclusion criteria but had started an SSRI within one month were included.

As part of the screening process prior to enrolment, individuals were asked if their current depressive illness was a first episode or a relapse.

Exclusion criteria

- Generalised learning difficulties.
- Pervasive Developmental Disorder.
- Pregnancy.
- Currently taking another medication that may interact with an SSRI and unable to stop this medication.
- Substance abuse.
- A primary diagnosis of Bipolar Type I, Schizophrenia or Eating Disorders.

Individuals who had received a psychological therapy consistent with the trial protocol for CBT, STPP or BPI were excluded.

Overall 470 individuals were recruited and provided written informed consent, as did their parents or guardians. Ethical approval was by the Cambridgeshire 2 research Ethics Committee, Addenbrooke's Hospital Cambridge, UK. Follow up was undertaken with

repeated reassessments at nominal points time periods set at 12, 36, 52 and 86 weeks after randomisation to evaluate recurrence of self-reported depressive symptoms and enable re-evaluation of clinical diagnosis of an episode of major depression.

Chapter 3

Measures

A multi method measurement approach of current mental state and psychosocial impairment was used. Measures for the adolescent patients included a selected set of self-report measures on current moods, feelings and behaviours, an interviewer-based assessment of current and previous psychiatric disorder completed by patients and a parent, an assessment of suicidal behaviour and non-suicidal self-harm behaviours and finally self-reported assessment of current cognitive ruminations and depressive cognitive style. The purpose of these measures was to test the primary and secondary hypotheses and to examine whether there were any moderating cognitive processes influencing treatment response or outcome.

Psychopathology

Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL)

The Kiddie-SADS Present and Lifetime (PL)-Version is a semi-structured interview measure which was used to establish the presence of DSM-IV diagnoses at all research assessments (baseline, 6, 12, 36, 52 and 86 week) (40). Each symptom is rated on a three-point scale of 1–3, 1 = non-clinical , 2 being sub-threshold and 3 being a clinically relevant symptom with the additional option of rating 0 = no information given to make a rating ,. Only symptoms rated as 3 were taken as clinically significant and DSM-IV criteria were used to ascertain the presence of current and past major and sub-threshold depression episodes. Patient and parents completed the measure and both interviews were used to construct a diagnosis based on positive symptom reporting from either respondent. Inter-interviewer agreement on the presence or absence of diagnoses has previously been assessed as satisfactory in adolescents with current mental illness (kappa, range for all diagnoses 0.7–0.85) (41) . The K-SADS-PL was also used to generate DSM-IV current comorbid diagnoses.

Mood and Feelings Questionnaire (MFQ)

The MFQ is a 33-item self-report measure completed by the adolescent of current depressive symptoms present over the past 2 weeks and was administered at all research assessments.

The instrument is designed to cover symptom areas specified in DSM-IV for an episode of major depressive disorder (42, 43). It has good test–retest reliability (Pearson's $r = 0.78$) (44) an α coefficient of 0.82 and discriminant validity for detecting an episode of major depressions in clinical adolescent samples (45). The MFQ is sensitive to change in depression over time (weeks and months) in adolescents with higher scores in well adolescents predicting episode onset(46, 47). It is scored on a 3 point likert scale of 0,1,2 giving a range of 0-66 and the higher the score the greater the likelihood of increased number and severity of depressive symptoms.

Revised Children's Manifest Anxiety Scale (RCMAS)

This self- -report questionnaire contains 28 items that measures current general anxiety, including physiological anxiety, worry/oversensitivity, and social concerns (48, 49). Scoring is on a 4-point Likert Scale and higher scores indicate greater levels of anxiety that may have trait like qualities (48, 49).

Short Leyton Obsessional Inventory (LOI)

The Short Leyton Obsessional Inventory (Child Version) is an 11-item, self-report questionnaire for current symptoms of obsessive-compulsive disorder (OCD) in children and adolescents(50). Internal reliability of the scale is high for the short scale total (Cronbach alpha =.86). It is scored on a 4-point Likert scale and higher total sum scores indicate greater obsessional thinking and compulsive behaviour.

Behaviours Checklist

The behaviours checklist is an 11-item self-reported checklist for symptoms of antisocial behaviour based on DSM-IV criteria for conduct and oppositional disorders. It is a self-report measure, scored on a 4-point Likert scale (12).

Classification Suicide Severity Rating Scale (C-SSRS)

This instrument is designed to track suicidal adverse events across a treatment trial (51). It is a prospective version of the system developed for the Food and Drug Administration of the

USA (FDA, www.**fda**.gov/downloads/Drugs/Guidances) as a way to get better safety monitoring and avoid inconclusive reporting of these events. Being feasible and of low-burden (typical admin time 5 minutes), it assesses both behaviour and ideation and appropriately assesses and tracks suicidal all events. It uniquely addresses the need for a summary measure of suicidality. The C-SSRS was administered in the form of an interviewer led respondent based semi-structured interview, at all time points, alongside the K-SADS-PL

The Risk-Taking and Self-Harming Inventory for Adolescents (RTSHIA)

The RTSHIA is based on existing instruments for assessing self-harm and risk-taking behaviour, and on clinical descriptions of these behaviours, using items that tap into these in both direct and indirect ways (52). The 20 items range from milder behaviours such as picking at wounds and pulling one's hair out to more serious SH such as taking an overdose and attempting to commit suicide. Most items contain the word "intentionally" or end with the phrase "to hurt or punish yourself". The items are on a 4-point Likert scale, referring to life-long history. The higher the score the greater the general risk-taking and self-harm and the 2 sub-scales (risk-taking; self-harm) can be scored separately. The instrument was administered at all time points.

Ruminative Responses Scale (RRS)

The RRS is a 39-item measure taken from the Nolen-Hoeksema's Ruminative depression questionnaire (35). It describes responses to low mood that are self-focused, symptom-focused and focused on the possible consequences and causes of the mood using a four-point Likert scale. Rumination is a potential cognitive vulnerability factor for depressive symptoms among adolescents (53). High rumination predicts onset of depressive disorder in healthy adolescents (54). (26). Preliminary data from the previous ADAPT RCT suggested that CBT may reduce rumination. Although this had no effect on depressive symptoms over 28 weeks, it may reduce relapse risk (36).

The Depressive Experience Questionnaire for Adolescents (DES-A) – Short Version

Adult patients with clinical depression may be characterized by putative cognitive style (37-39). This cognitive style has been described as generically one of immaturity characterised and manifest by an excessive preoccupation with relatedness with others (principally focused on disappointment with relationships) and self-definition or identity (principally focused on self-criticism). In this study relatedness and identity were measured by the short version of the Depressive Experiences Scale for Adolescents (55).

The RRS and DES-A scales were completed prior to randomisation. Planned use was to determine individual differences in the baseline total score of the RRS and the sub-scale scores for relatedness and self definition/criticism of the DES-A, and to test if they acted as potential moderators of treatment effects.

Health of the Nation Outcome Scales for Children and Adolescents (HONOSCA)

The HoNOSCA is a routine outcome measurement tool that assesses the behaviours, impairments, symptoms and social functioning of children and adolescents with mental health problems (11, 56, 57). It provides a global quantitative measure of an individual's current mental health status. The instrument consists of 13 scales. Each scale is interviewer-rated on a score between 0 and 4 (total range 0–52). The higher the sum and sub scale scores, the greater the level of overall mental health problems within the adolescent. The measure is sensitive to change in mental state and psychosocial functioning over a brief (weeks and a few months) period. The measure was used at all time points as a semi-structured interview with both subjects and parents. The measures planned use was as a correlate and adjunct to self-reported depression scores revealing the level of personal impairment for each patient over time.

Health economic ~~evaluations~~measures

Child and Adolescent Service Use Schedule (CA-SUS)

Data on use of all services included in the study were collected using the Child and Adolescent Service Use Schedule as previously used in the ADAPT study (32). Information

about the study participant's use of services was collected in by an interviewer at baseline and at 6, 12, 36, 52 and 86 week follow-up assessments with adolescent and parent. At baseline, information covered the previous three months. At each of the follow-up interviews, service use since the previous interview was recorded; in this way, the entire period from baseline to final follow-up was covered. The CA-SUS asks participants for the number and duration of contacts with various services and professionals. At each treatment contact, BPI, STPP and CBT therapists recorded information on the details of the treatment session including the start and end time and attendance. ~~.Data on the trial interventions, BPI, STPP and CBT were collected from clinical records.~~

EQ-5D

The EQ-5D™ is a standardised instrument for use as a measure of health outcome (http://www.euroqol.org). Quality adjusted life years (QALYs) were calculated from EQ-5D scores taken at baseline, 6, 12, 36, 52 and 86 week follow-up interviews. The EQ-5D is a non-disease-specific measure for describing and valuing health related quality of life and it includes a rating of own health in five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), plus a rating of own health by means of a visual analogue scale (a "thermometer") (0-100)(58). A recent study provided initial evidence to support the relevance of the EQ-5D in adolescents with major depression (59) and it was used successfully in a previous study of treatment for adolescent depression in the UK (32). QALYs were calculated using the area under the curve approach after the health states from the EQ-5D were given a utility score using responses from a representative sample of adults in the UK(60). It is assumed that changes in utility score over time followed a linear path (61). QALYs in the second year were discounted at a rate of 3.5% as recommended by NICE (62).

Chapter 4

Ascertainment

The trial recruited patients from 3 regional centres and utilised local Child and Adolescent Mental Health Service (CAMHS) teams within those sites for trial recruitment. The local CAMHS teams (n=16, 5 or 6 in each regional centre) were visited by Principal Investigators based within their regional academic centre and had the study plan introduced to them. Three seminar days, one in each regional academic centre, were run to introduce the study design and planned recruitment procedures to clinical staff and service managers. NHS staff had the opportunity to inform the recruitment process, ask questions about the science, the design and the objectives of the trial. Each clinic that was involved designated a clinical staff member to champion the study to other staff on a weekly basis to encourage recruitment invitations to patients. Identification and initial screening of potential participants was conducted by clinical staff working within these clinics.

All study participants were identified from routine NHS specialised (tier 3) referrals to the participating CAMHS clinics. There were no special recruitment strategies unique to the study, and no use of advertisement. At first assessment to CAMHS the assessing clinicians were invited to complete a depression symptom screen designed to assist referral to IMPACT. Using a combination of routine clinical methods at first assessment aided by a depression screen based on DSM-IV criteria potential cases were identified as being in scope for the study. The assessing clinicians informed the young person and their parents/carers about the trial and invited them to consider taking part. If an expression of interest to take part was obtained their details were passed to the research group. They were informed at this point that the study team would be in touch if they expressed an interest to participate. The potential participants were informed that recruitment was dependent on the research team assessments and whether or not the patient met the inclusion and the exclusion criteria.

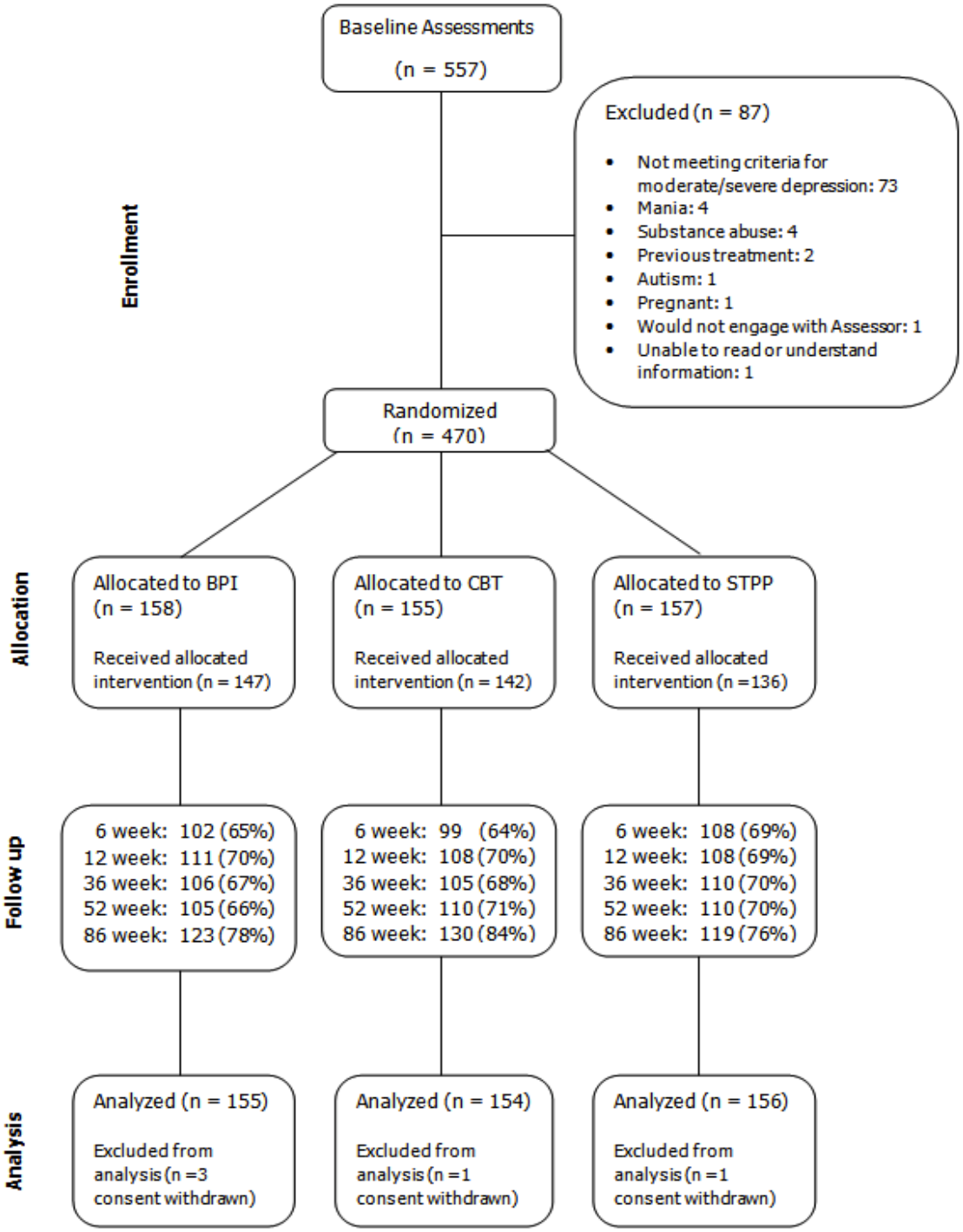
The participants and their parents or legal guardians were sent information sheets about the trial and a reply envelope indicating they had read the information and were willing to be

contacted by a researcher who then scheduled an initial meeting during which the participants were invited to sign a consent form. In line with good clinical practice, young people under 16 consetned along with their parents but those who did not wish to involve their parents or carers were encouraged to do so. 16 or 17 year olds who had capacity and did not want parents or carers involved but met criteria were included.

Two research workers working in parallel sessions administered all research baseline assessments to the young person and their parent(s)/carer(s). After this, researchers confirmed whether the participants met diagnostic and other entry criteria. Where there was uncertainty, parent/carer report, where available, was combined with the young person's responses and, if still not clear, a consensus discussion was held with the local PI to establish eligibility. If they met criteria and gave consent, participants were randomised remotely into one of the treatment arms. The trial co-ordinator in each regional site then informed the young person and the referring clinic about the treatment allocation. Other researchers, some of whom conducted follow up assessments, remained blind to treatment allocation. Following randomization, trained and supervised CAMHS staff working in the participating clinics treated all patients in the trial.

The study sample recruitment procedure is shown in Figure 2.

Figure 2: Consort diagram of patient ascertainment for the IMPACT study



A total of 470 patients from 557 baseline assessments aged between 11 and 17 were recruited and randomised. Of these, five subjects withdrew consent and have had their study records destroyed (two from N London and three from the North West). There was no indication that this was related to treatment allocation. Of the remaining 465 randomised patients, 185 (40%) were from East Anglia, 127 (27%) were from North London and 153 (33%) were from the North West, respectively. A total of 348 (75%) were girls.

Chapter 5

Trial procedures

The IMPACT trial compares three psychological interventions: Short Term Psychoanalytic Psychotherapy (STPP), Cognitive Behaviour Therapy (CBT) and Brief Psychosocial Intervention (BPI) delivered to treat an episode of DSM-IV major unipolar depression and to reduce the risks of recurrence of depression through reducing symptom levels over the follow-up period of 36-86 weeks.

After consent had been obtained and the baseline assessment had been carried out, a trial ID was assigned. Randomisation was stratified by age, sex, regional centre and a minimal score on the Mood and Feelings Questionnaire (MFQ) of 23 indicating high likelihood of meeting MDD criteria or sub-threshold disorder with impairment (63).

Randomisation to treatment arms was conducted online by the trial coordinator, after allocation of the trial ID, thus ensuring allocation concealment. Information about treatment allocation was forwarded to a clinic champion who ensured allocation of a therapist to the participants. To minimise bias that could arise from knowledge of treatment allocation the outcome assessors were blind to treatment allocation and did not communicate with each other or with therapists about case assessments. All interviews were audiotaped and a random sample re-rated by independent raters. If blindness was broken, an alternative assessor carried out all subsequent assessments.

Planned interventions

IMPACT was a pragmatic superiority trial comparing the relative clinical effectiveness of three psychological treatments each with evidence of clinical efficacy being associated with clinical remission in the short term (i.e. 3-6 months) . These treatments are available in CAMHS NHS practice although distribution around the UK is not standardised. The three treatment approaches tested in this study were all manualised.

A duty of care by clinical staff to patients was observed in all clinical arms. This included parent support and engagement, explanation of treatment principles, maintenance and support

of family during individual treatment, individual risk management strategies and contact with other agencies where appropriate.

Comprehensive treatment protocols were developed for the trial and designed for delivery by practioners working in routine NHS CAMHS settings. The rational for using treatment manuals as guides to therapy is that:

- Manuals aid dissemination of treatment methods into clinical practice.
- They help to standardize the intervention between therapists and across site.
- They form the basis for audiotape ratings of treatment adherence and differentiation and thus ensure that the interventions have been given properly in keeping with the trial protocol.

The three treatments differed in the total number of sessions they offered over the study period. The number of sessions offered for each treatment were as follows:

- BPI - 12 individual sessions plus up to 4 family/parent sessions to be delivered over 20 weeks.
- STPP - 28 individual sessions plus up to 7 parent sessions to be delivered over 30 weeks.
- CBT - 20 individual sessions plus up to 4 family/parent sessions to be delivered over 30 weeks.

The treatments are described below.

1. Brief Psychosocial Intervention (BPI)

Brief Psychosocial Intervention (BPI) is a brief structured intervention for the treatment of unipolar major depression in adolescents (64) (65). The brief psychosocial care approach originally used in the ADAPT RCT was the basis for BPI used in this trial (11, 23, 26). In the ADAPT study, the forerunner of BPI (described as non-manualised treatment as usual [TAU] in CAMHS) together with Fluoxetine 20mg-60mg daily, was as effective as TAU+Fluoxetine+CBT for moderate to severely depressed adolescents in routine NHS practice (11, 26). This brief psychosocial approach was reformulated for the current study and formalised into a treatment manual (23). Prescribing an SSRI is not a part of BPI per se but can be added and fully integrated if improvement is not judged to be occurring after 2-4 weeks as per the NICE guidelines of 2005 (12).

Meta analytic studies of adolescent psychotherapies highlight the central therapeutic importance of care that is structured, evidence driven and founded on interpersonal effectiveness, warmth and trust (66, 67). The incorporation of collaborative care for depression in adults has been shown to provide added value for the treatment of depression in adults over above psychological and or medication treatments (68, 69).

The BPI treatment manualised for this study emerged from the treatment as usual in ADAPT.The intervention is a treatment base don re-structuring and codification of the principles and practises found in the domains of skilled assessment, listening, information giving, advising, problem solving, safety, caring and explaining about adolescent depression.

BPI was delivered in this study as the standard control psychosocial intervention. Emphasis was placed on the importance of psychoeducation about depression, and action oriented, goal-focused and interpersonal activities as therapeutic strategies. Specific advice was given on improving and maintaining mental and physical hygiene, engaging in pleasurable activities, engaging and maintaining schoolwork and peer relations and diminishing solitariness. BPI did not use cognitive or reflective analytic techniques. There was therefore no discussion of unconscious conflict and no deliberate effort to modify maladaptive models of attachment relationships. Neither was there any focus on changing cognitions and negative cognition-driven behaviours were not deconstructed. BPI consisted of up to 12 individual sessions plus up to 4 family/parent sessions delivered over 20 weeks. Liaison with external agencies and personnel e.g. teachers, social care and peer group were commonly undertaken.

Case management in BPI

Since BPI case management has a rational and relational framework case management is founded on the three principles of:

- Interpersonal effectiveness.
- Understanding of mental states.
- Activation and problem solving.

The case management process is integrated through the development of a formulation which is a general construct summarising the probable relationship between the above 3 constructs. The formulation is developed as a series of prospective working hypotheses that can be tested

and evaluated against subsequent progress within the therapy. BPI is delivered within this framework in up to 12 sessions plus up to 4 family/parent sessions over 20 weeks.

Therapy was delivered with the following strategies and principles being utilised throughout.

- Effective engagement, activation and problem solving.
- Diagnostic accuracy, and mental state evaluation.
- Sharing understanding and knowledge of the impairments and consequences of symptoms; the "lived experience" including effects in other settings such as school or peer relationships.
- Attention to accuracy in conducting a risk assessment and its management.
- Sharing aetiological description: defining risk and protective factors.
- A psycho-educative approach that at all points aims to help "activate" and empower, including parents and family as necessary.
- An approach that includes understanding of the role of medication, its appropriate use and how it sits within the care package
- A jointly agreed, collaboratively developed, and shared, management plan
- All delivered in a fashion that can help the child, young person and parents to manage and cope with their emotional expression.

Therapists, training and supervision

BPI therapists in this study were drawn from a range of professional backgrounds including mental health nursing, clinical psychology, psychiatry and mental health social work. The majority (>80%) of therapists were however psychiatrists in specialist CAMHS training as well as consultants. In the IMPACT trial to be eligible for training as a BPI therapist clinicians had to:

- Have had a minimum of 6 months supervised or independent work in a multidisciplinary child and adolescent mental health setting.
- Have already established sufficient competence and skills to be allowed to undertake independent mental health assessment and treatment of adolescents with moderate to severe depression.

BPI practitioners had basic training in BPI: reading of the manual; confirmation by the supervising clinician that they met the criteria to become an BPI therapist; attendance at a BPI training day; continued access to the BPI manual and ongoing supervision fitting in with usual local CAMHS NHS supervisory structures. The regional leads for BPI met and problem solved supervisory issues in relation to BPI on a regular basis across the IMPACT study period.

2. Short Term Psychoanalytic Psychotherapy (STPP)

Psychoanalytic psychotherapy with children and young people is a well-established specialist treatment for emotional and developmental difficulties in childhood and adolescence, with an emerging evidence-base (70, 71). It is one of several psychological therapies recommended by NICE as equally effective in the acute treatment of child and adolescent depression (72). Its intellectual roots are drawn from psychoanalysis, child development, attachment theory and developmental psychopathology.

In this trial all therapists were approved as psychoanalytically trained by the Association of Child Psychotherapists UK. The short-term model of psychoanalytic psychotherapy (STPP) used shares therapeutic principles with time-limited psychodynamic work for adults with depression for which there is now a substantial evidence-base (70). It is a 28-session model, with parents or carers being offered up to 7 additional sessions by a separate parent worker. STPP aims to elaborate and increase the coherence of the young person's mental models of attachment relationships and thereby improve their capacity for affect regulation as well as the capacity for making and maintaining positive relationships with other (73).
The STPP method (70, 74)draws on a long history in the UK of psychoanalytic work with depressed children and young people (75) including an unpublished manual used in an earlier clinical trial, in which short-term psychoanalytic psychotherapy for children with depression demonstrated good outcomes (34). As with the other manuals used in the IMPACT study, the STPP manual (71) provided a guide to practice but not a recipe or a step-by-step guide, and drew on the existing skills and training of child and adolescent psychotherapists already working in the NHS.

STPP aims to elaborate and increase the coherence of the young person's mental models of attachment relationships and thereby improve their capacity for affect regulation as well as the capacity for making and maintaining positive relationships with others. When treatment is

successful, it should free the young person to engage in normal adolescent development including educational attainment and independent peer group development involving a degree of separation from their primary carers (76).

The techniques of child and adolescent psychotherapy are primarily based on close and detailed observation of the relationship the child or young person makes with their therapist. The therapist introduces the therapeutic task to the young person as one of understanding feelings and difficulties in their life. The therapist's stance is non-judgemental and enquiring and conveys the value of understanding: the aim is to put into words conscious and unconscious thoughts and feelings. Through actions and words, the therapist attempts to convey an openness to all forms of psychic experience – current preoccupations, memories, day-dreams, nocturnal dreams and phantasies – but will be attuned specifically to evidence of unconscious phantasies which underlie the young person's relationship to self and others. This attentiveness to unconscious phenomena is specific to psychoanalytic psychotherapy, and is related to the theoretical importance attributed to these deeper less accessible layers of the mind.

With all adolescents, most particularly those with difficult early years' experiences, there is a need for the therapist to be in a state of mind characterised by availability to the reception of projected contents (anxieties, affects, uncertainties) of the adolescent's mind. The patient's experience of the therapist receiving, holding in mind, and thinking about this projected material is a central feature of the therapy. The adolescents are helped to gain ownership of previously disowned part of themselves, and are strengthened by identification with another person (i.e. the therapist) experienced as capable of making meaning in this way and thus enabling more mature thinking to take place.

The STPP therapist and/or parent worker requires an alertness to the need, at times, for active communication and liaison with other significant individuals and agencies in the adolescent's life. This may include external agencies such as school/college, youth and social services, and also mental health colleagues, including Child and Adolescent Psychiatrists, where there are issues about risk and a possible need for medication or hospitalization. Prescribing an SSRI is not a part of STPP per se but can be added and fully integrated if improvement is not judged to be occurring after 2-4 weeks as per the NICE guidelines of 2005 12.

Support for parents or carers, offered concurrently and in parallel with individual therapy for children and adolescents, is a well-established practice in the UK. There is some evidence

that psychoanalytic therapy is more effective when undertaken with concurrent parent support work (71). Parent support aims to help with parental anxieties and develop greater understanding about their relationship to their son or daughter.

Therapists, training and supervision

To be eligible to practice as an STPP therapist in the IMPACT study the clinician had to:

- Have undertaken a four-year postgraduate professional training, leading to membership of the Association of Child Psychotherapists (ACP) or be fourth-year trainee members of the ACP.
- Those doing parent work were individuals with at least 6 months CAMHS experience following professional training in child psychotherapy, clinical or counselling psychology, child mental health nursing, family therapy or psychiatry.

STPP training was designed and delivered on the basis that prospective STPP practitioners already have all the fundamental competencies and skills required to deliver all the components of STPP. Building upon these existing skills STPP training for IMPACT comprised: reading of the STPP manual; confirmation by the clinician that they met the criteria to become an STPP therapist; and attendance at an STPP training day.

STPP supervision by a consultant Child and Adolescent Psychotherapist was provided as part of routine practice within the CAMHS team.

3. Cognitive Behaviour Therapy (CBT)

Cognitive Behaviour Therapy (CBT) therapy in this trial is based on the classical form originally developed for adults with depression. This posits that emotional disorders are characterised by pervasive information processing biases which increase vulnerability to depression in the context of environmental stress, and which maintain and amplify core symptoms of depression including hopelessness, low mood, and irritability. The focus of CBT is to identify the information processing biases that maintain depression and low mood and to amend these through a process of *collaborative empiricism* between the therapist and client.

It was adapted for this study to include parental involvement, a large focus on engagement and an emphasis on the use of behavioural techniques. (77, 78). CBT included up to 20 sessions plus up to 4 family/marital sessions over 30 weeks. CBT therapists were routine CAMHS clinicians and were either clinical psychologists, or other clinicians who had received post qualification training in CBT. CBT emphasizes 'collaborative empiricism': i.e. explicit, tangible and shared goals between therapist and young person, and clear structured sessions. CBT links thoughts, feelings and behaviours and techniques includes behavioural activation ; identifying and challenging negative automatic thoughts; developing adaptive thoughts and relapse prevention. Topics introduced within a therapy session are extended and supported outside the session by tasks completed by the client between sessions and reviewed at each subsequent session. CBT was delivered to the adolescent alone or to the young person and parent(s) flexibly. A formulation was developed at the start of therapy which included consideration of parental and family factors in the development and maintenance of depression. Where it was considered relevant parent(s) were involved in therapy session, by negotiation, to support the young person in treatment.

In this study CBT was manualised and incorporated adaptations for working with adolescents (as opposed to adults) including inclusion of simplified and aged appropriate cognitive techniques as well as the flexibility to take a behavioural focus if cognitive work was considered too demanding for a young person. A number of additional amendments were made including a greater focus on engagement in therapy, on building the therapeutic alliance, and on working collaboratively with parents and schools. Parents were involved in treatment sessions as indicated by the formulation and the preferences of the family. There were no separate sessions for parents.

Treatment length for CBT was a maximum of 20 sessions, delivered weekly, tapering to every 2 weeks as needed for relapse prevention, plus up to 4 family/parent sessions. Sessions were structured with an agenda set by the therapist and young person at the start of every session and out of session assignments agreed between the therapist and young person. Typically, early sessions (1-4) focused on relationship building, understanding the young person's current presentation and experience, and psycho-education, including the CBT model. A provisional formulation of the young person's difficulties, incorporating family history, key life events and transitions, recent stressors, and coping strategies was developed with the young person (and parent where relevant). Subsequently the formulation guided

treatment. This included using CBT techniques to treat non depressive comorbid symptoms oo anxiety, obsessions and compulsions and oppositional behaviours.

Mid-treatment focused on identifying and modifying the behavioural and cognitive processes that maintained depression and low mood for that young person. Behavioural work included activity scheduling, ratings of mastery and pleasure and reinforcement of engagement in activities. Cognitive work included identifying dysfunctional and unhelpful automatic thoughts and thought challenging using a range of techniques including behavioural experiments. Modifications to the core CBT model, such as the use of mindfulness were permitted depending on the individual formulation. The end of treatment was marked by a focus on relapse prevention. Typically this included a revisit to the formulation, identifying potential risk and vulnerability factors, problem solving, and building resilience. Prescribing an SSRI is not a part of CBT per se but can be added and fully integrated if improvement is not judged to be occurring after 2-4 weeks as per the NICE guidelines of 2005 12.

Therapists, training and supervision

CBT therapists were NHS staff from a range of professional backgrounds including clinical and counselling psychology, nursing, and occupational therapy. They delivered CBT for depression as part of their routine clinical practice in multi-disciplinary Child and Adolescent Mental Health services.

CBT therapists had to have received specialist training in CBT, either as part of their core professional training (i.e. as a clinical psychologist) or as post qualification training (i.e. as a nurse or occupational therapist). They were eligible to be IMPACT CBT therapists if they routinely used CBT in their NHS clinical work and if they could demonstrate some pre or post qualification training in CBT.

CBT training was delivered as a one day workshop within services. It was designed as a top-up training for individuals who already had core CBT skills. The core features of the treatment manual were described and the practicalities and constraints of delivering CBT within the context of a research trial were discussed. All clinicians had copies of the CBT manual and familiarised themselves with it .

CBT supervision was provided as part of routine practice within the CAMHS team.

Prescribing of Fluoxetine during the trial

For all three arms Fluoxetine or another SSRI could be added where clinicians judged that combination therapy may accelerate the time to remission following NICE guidelines for a major depression episode in adolescents (12). A test dose of 10 mg was given for 48 hours followed by 20 mg as a single dose. If there was no improvement within 2-4 weeks the dose can be adjusted upwards to 60 mg maximum.

Chapter 6

Treatment adherence and differentiation for each therapy modality

Establishing treatment differentiation between the three interventions, and treatment adherence to each manualised intervention, are essential validity steps toward interpreting the relative effectiveness of different treatment approaches. This chapter describes theory, its application to this study and provides results of the reliability and validity tests applied to audiotape measures of adherence to protocol for each therapy and differentiation of therapies from each other.

Treatment adherence refers to 'the extent to which a therapist used interventions and approaches prescribed by the treatment manual, and avoided the use of intervention procedures proscribed by the manual' [1]. Adherence in this study is therefore not measuring the overall clinical competence of each therapist. The key task addressed is to answer the question "Did the therapy occur as intended by the manual?" (treatment adherence), and additionally, "was each of the treatment arms sufficiently distinct from the others in regards to the techniques used?" (treatment differentiation). Establishing adherence to the manualised therapy, and differentiation between the treatment arms, are essential validity step toward interpreting the relative effectiveness of different treatment approaches, which is key to the primary and secondary objectives of this study.

The aim of the adherence and differentiation study was therefore to assess:

- The degree to which the therapists utilize prescribed or proscribed procedures, based on the treatment manual used in each arm of the study ('treatment adherence').
- Whether treatments differed from each other along critical dimensions ('treatment differentiation').

Design

Two independent raters, blind to treatment allocation, rated each treatment session from the three treatment modalities, using the Comparative Psychotherapy Process Scale (CPPS), which is a widely-used measure of therapeutic techniques in psychodynamic and cognitive-behavioural therapies (79). These ratings were used to assess treatment adherence for the CBT and STPP arms of the study, and treatment differentiation between all three arms of the study. In addition, sessions from the BPI arm of the study were each rated by two raters, using a newly-devised BPI adherence measure, in order to assess treatment adherence to the BPI manual. Double ratings were used to check the reliability of each measure and improve the precision of the estimate for each tape.

Sample size

All therapists and young people in the IMPACT study agreed to their sessions being tape recorded for the purposes of the fidelity and differentiation analysis. Recorded sessions were categorised as either 'early' or 'medium/late' in therapy. A random sample of 232 tapes (76 CBT tapes, 81 STPP tapes and 75 BPI tapes) were selected and stratified by modality and timing (`early', i.e. the first third of therapy, or 'medium/late', i.e. the middle or last third of therapy), and were then rated on the measure of comparative (psychodynamic and cognitive-behavioural) techniques. The slight difference in the number of sessions rated by arms arose due to the number of tapes available by treatment arm and site. As the comparative measure did not include the active features of BPI, the 75 BPI tapes were additionally rated on a treatment-specific measure.

The 75 BPI tapes were additionally rated on the BPI-specific measure.

Instruments

Comparative Psychotherapy Process Scale – External Rater form (CPPS-ER)

The CPPS is a measure that assesses the degree to which a therapist uses techniques of psychodynamic-interpersonal (PI) and/or cognitive behavioural psychotherapy (CB) in an entire psychotherapy session (79). Developed from an extensive empirical review of the comparative psychotherapy process literature (79) all items are rated on a 7-point Likert

Scale, ranging from 0 (“not at all characteristic”), 2 (“somewhat characteristic”), 4 (“characteristic”), to 6 (“extremely characteristic”). The 20-item measure includes ten PI items and ten CB items, forming two distinct sub-scales. The psychometric properties of the CPPS have been well established in psychotherapy with adults (79). Internal consistency of both scales has been good to excellent: Cronbach’s α of .82 to .92 for the PI scale and .75 to .94 for the CB scale (79, 80). Inter-rater reliability is reported as rating from good through to excellent (ICC 0.6 to 0.75) (80, 81).

In the current study, the CPPS was used to assess treatment adherence for the CBT and STPP arms of the study, and to assess treatment differentiation between all three treatment modalities used in IMPACT. Overall, a CBT therapy session was judged to be ‘adherent’ if the total mean score for items on the CB sub-scale of the CPPS was 2 or above, where a mean score of 2 indicates that the use of CB techniques was 'somewhat characteristic' of a session. An STPP therapy session was judged to be ‘adherent’ if the total mean score for items on the PI sub-scale of the CPPS was 2 and above, where a mean of 2 indicates that the use of PI techniques was 'somwhat characteristic' of a session.

The CPPS could not be used to rate treatment adherence for BPI, as it does not have a BPI sub-scale; however it could be used to rate treatment differentiation between BPI and the other two therapies, as ratings of BPI sessions using the CPPS could be used to determine whether BPI clinicians were making use of techniques which were not part of the BPI manual, but were associated with the specialist psychotherapies, whether psychodynamic (the PI sub-scale) or cognitive-behavioural (the CB sub-scale).

Raters were all post-graduate psychologists, who were blind to treatment allocation. A total of seven raters went through approximately 30 hours of training on the measure, until they were able to demonstrate a high level (>80%, for each pair of raters) of inter-rater reliability. Each session was watched in its entirely, with the rater blind to treatment arm, and then rated by the two judges independently.

Brief Psychological Intervention Scale (BPI-S)

The BPI-S is a new scale, developed specifically for use in this study to assess treatment adherence to BPI. The 18 key components of the BPI manualised treatment were identified using expert consensus in the IMPACT team. A pilot investigation conducted by the BPI experts used a sample of 5 tapes to develop the adherence scale. Following this phase the

measure was operationalised as an 8-item measure with 3 ‘core’ and 5 ‘general’ items, rated as a likert-scale (0 – no evidence, 1 – passing evidence, 2 – some evidence, to 3 –clear evidence).

The three core items are: (i) activation and problem solving; (ii) interpersonal effectiveness; and (iii) attention to mental state-current presentation or diagnosis. The five general items are: (i) Attention to vulnerability and protective factors, (ii) Psycho-education; (iii) Setting case management within a BPI framework; (iv) Attending to the social context of the patient; and (v) Making effort to help the patient manage their emotional expression. These eight items were chosen to (a) capture important treatment principles (relevance), based on the BPI manual; and (b) cover all relevant treatment principles (comprehensiveness), as outlined in the BPI manual.

For each item, a score of two or more was considered an adequate level of adherence. Overall, a BPI therapy session was judged to be 'adherent' if:

i. At least 2 out 3 ‘core’ items were rated as 2 or above

ii. And a total of at least 4 out of the 8 items were rated as 2 or above.

When this revised standard was applied to the 5 taped sessions previously rated, 100% agreement was obtained between the experts who rated 4 sessions as adherent and 1 session as not adherent.

Training for 5 independent raters was completed over two days. The raters were all trained in BPI and experienced senior clinicians with medical and psychiatric qualifications, and achieved high levels of inter-rater reliability (>80%), by the end of the training. Feedback from the raters during the training process indicated high levels of face validity indicated by good comprehension of the BPI adherence scale and an understanding of the rating measure and procedure. Each session was watched in its entirely, and then rated by the two judges independently; but raters were not blind to the treatment arm, as only BPI sessions were rated using the BPI-S. The results of the reliability and validity analyses are given in chapter 9.

Chapter 7

Moderation of treatment response

Little is understood regarding factors that may influence treatment response in depressed adolescents. This study included 2 putative cognitive processes that the literature suggests may moderate therapeutic response to psychological treatments. These are:

i) Individual differences in self-reported ruminative thinking whilst depressed. A ruminative response style is defined as persistently brooding or dwelling on current depressive thoughts and feelings, often to the exclusion of other themes in the patient's life (35).

ii) The quality of predominant depressive experiences which is defined as possessing a thinking style (dependent or self-critical) likely to predispose or be associated with depressive illness but not synonymous with a pattern of symptoms (37).

Ruminative response style

Rumination is the compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions (82). Rumination is similar to worry except rumination focuses on bad feelings and experiences from the past, whereas worry is concerned with potential bad events in the future (83). Both rumination and worry are associated with clinical anxiety and depression (83).

Rumination has been widely studied as a cognitive vulnerability factor for depression, however its measures have not been unified (83). In the Response Styles Theory proposed by Nolen-Hoeksema (84) rumination is defined as "compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions". Because the Response Styles Theory has been empirically supported, this conceptual model of rumination is the most widely used.

Extensive research on the effects of rumination, or the tendency to self-reflect, shows that the negative form of rumination interferes with people's ability to focus on problem-solving and

results in dwelling on negative thoughts about past failures (85). Evidence further suggests that the negative implications of rumination are due to cognitive biases, such as memory and attentional biases, which predispose ruminators to selectively devote attention to negative stimuli (86). Such negative biases resulting in critical self-devaluing thinking and can be found in dysphoric adolescents with no history of depression but with a childhood temperamental style characterised by being easily distressed and fearful but likely to be followed by a relatively rapid return to calm mood (87). Depressed adolescents who have high rumination scores are more likely to show persistent depression and demonstrate impairments in autobiographical memory retrieval (88-90). Inducing ruminations in adolescents also results in increased depressive symptoms as there is a bias to ruminate on prior negative life events (41, 88, 89).

In this Trial self-reported rumination scores were measured by the ruminative responses styles questionnaire developed by Susan Nolen-Hoekseema and colleagues and validated independently(91). The scale was completed prior to randomisation and planned use of the baseline raw sum score as potential moderator of treatment effects was designed prior to analysis.

Hypothesis

1) Elevated RRS scores at baseline will be associated with lower treatment response in all arms and higher MFQ scores over the follow up period 36, 52 and 86 weeks.
2) Higher scores will show a better treatment response in the CBT compared to the BPI and STPP arms.

Depressive experiences style

Both theoretical assumptions and empirical findings suggest that adult patients with clinical depression may be characterized in terms of immaturity of cognitive styles e.g. (39, 92) (93) (38) which manifest as excessive preoccupation with relatedness (principally focused on disappointment with relationships) and self-definition or identity (principally focused on self-criticism). Research has provided empirical evidence for the assumption that individuals with depression may be predominantly troubled by one of the following issues:

i) High concerns about the quality of interpersonal relatedness with feelings of emptiness and loneliness, and intense fears of being abandoned and left unprotected.

ii) Possessing an extremely self-critical attitude together with feelings of worthlessness, guilt, failure, and self-blame.

Two psychometrically relatively robust factors have been shown to emerge across a number of studies (94). One factor, which may be termed ***dependent/relatedness*** is elevated by disruptions to rewarding affiliative interpersonal relationships. This is expressed primarily in dysphoric feelings following experiences characterised by personal loss, abandonment and being alone. The other is termed **self-critical/identity** and is elevated due to perceived personal failure and worthlessness. This is expressed in dysphoric feelings emerging in individuals who have a bias toward perfectionism, but are vulnerable to criticism both from others and from themselves.

Clinical evidence has accumulated on the difference in the responsiveness to different kinds of psychological treatment and their capacity to achieve therapeutic gain (Blatt et al., 2010; Blatt & Shahar, 2004). Clinical research with depressed adult patients has indicated that elevated levels of the self-criticism factor at baseline are associated with poorer therapeutic outcome at termination of therapy and at 3 month follow up in brief treatments for depression(93, 95). In contrast the dependent factor interfered with therapeutic progress primarily in the second half of the treatment process (in the last 8 weeks) by disrupting patients' interpersonal relationships both within and external to the treatment process (39, 92).

In this study the short version of the Depressive Experiences Scale for Adolescents (self-report) was used to measure relatedness and identity (55). The scale was completed prior to randomisation. Baseline sub-scale scores for relatedness and differentiation were tested as potential moderators of treatment effects.

The dara analytic moderator strategy is described in chaper 8 and results are presented in Chapter 9.

Chapter 8

Sample size and power calculation

This trial compares therapist-delivered treatments. In order that it has generalisability it has been suggested that statistical models of outcome estimate between-therapist variations (96). Personal characteristics and skills of individual therapists mean that outcomes for different patients seen by one therapist (within-therapist variance) are likely to be more strongly correlated than outcomes of patients treated by different therapists using the same treatment approach (between-therapist variance). This is measured as intra-therapist correlation coefficient (ITCC). If ITCC is not adjusted for, variance estimates will be too small, leading to type 1 error. Analysis of data from the ADAPT trial gave an estimate of the intra-therapist correlation coefficient (ICC) after adjustment for baseline covariates of zero at 28 weeks for the self-reported level of recent (2 weeks) depressive symptoms, the Mood & Feelings Questionnaire (MFQ). Given that estimates of ICC are imprecise sample size and power estimation considered values of the ICC of 0.025 and 0.05 as a sensitivity analysis. Methods for sample size calculation are described by Walwyn & Roberts (97).

The ADAPT trial gave an SD of 14.6 at 28 weeks follow-up and correlation between baseline and follow-up of 0.41 for MFQ. We have assumed 5 points on the MFQ to be the minimum clinically important difference, which is justified in three ways:

(i) This is approximately 25% of the change in the MFQ scale from baseline to 28 weeks observed in ADAPT.
(ii) It is also equivalent to a 1point improvement on 5 of the 33 items of the scale.
(iii) It is a standardised effect size of 0.34 (small to medium) (98).

The primary analysis of the trial involved, first a comparison of the two specialist treatments, CBT and STPP and secondly a comparison of the two specialist treatments combined against BPI. A 2.5% two-sided significance level was therefore used for the sample size calculation. The ADAPT trial had 92% follow-up at 28 weeks and so 90% follow-up was assumed. Statistical analysis was planned to adjust for baseline. Sample size calculation was adjusted for this assuming a correlation of 0.41 between baseline and follow-up estimated from data in the ADAPT trial.

In each of the three regional centres six CAMHS units would be recruited with each unit having at least one therapist for the three treatment modality being compared. The target patient recruitment for each clinic was 30 patients giving 10 patients per treatment modality per clinic and a total sample size of 540. With these assumptions, the power for the comparison of CBT with ST was 84% if the ICC was zero ,76% for an ICC of 0.025 and 69% if it was as large as 0.05. For the comparison of the specialist treatments (CBT & STPP) with BPI the power was 93% 88% and 82% for an ICC of 0.0, 0.025 or 0.05 respectively.

Data analytic strategy

Statistical analysis of the three randomised treatment groups was based on the intention-to-treat principle subject to the availability of data. Statistical analyses were carried out using STATA Release 13 (99).

Data cleaning of outcome and baseline data was conducted without the treatment group allocations in view. Many of the outcome measures were patient completed or interviewer-rated psychometric instruments. Where there were missing item-level data, these were imputed by replacing the missing item by the mean of the other available items for that occasion provided at least 50% of items had been completed (pro-rating).

Summary statistics of outcome data were reviewed by the trial research team to identify data errors prior to revealing treatment allocation.

Analysis of the primary outcome measure and continuous secondary outcome measures

Characteristics of the study sample are reported using standard frequency measures and summary statistics. Preliminary inferential analysis investigated the pattern of missing outcome data comparing baseline characteristics of subjects with and without follow-up data using a logistic regression model.

Whilst time of assessment was scheduled at 6, 12, 36, 52 and 86 weeks, there was substantial variation in timing of assessment compared to randomisation leading to some overlap between assessment intervals of consecutive assessments. To prevent bias due to assessments being delayed we have used time since randomisation as a continuous variable in

a longitudinal mixed model rather than the notional assessment point. Random effects were included for *between subject* variation in the intercept and time gradient of the subject. As there may be variations in patients outcomes a *between therapists* random effect term was added to the models. Where a participant's therapist was not known or they received no therapy, the participants identifier code was used as the therapist code instead. Fixed covariates were included to model systematic differences due to treatment, the time with treatment interaction and pre-specified participant characteristics at baseline (see Table 1).

Table 1: Fixed covariates for each model

Measure	Type of Measure	Data Collection Method	Fixed Covariates
Primary			
MFQ	Continuous	Self-report	Baseline MFQ, LOI, ABQ scores, treatment allocation, region, sex, age at randomisation, co-morbid behaviour disorder^{+}, prescription of SSRI before trial entry.
Secondary			
RCMAS	Continuous	Self-report	Baseline RCMAS, LOI, ABQ scores, treatment allocation region, sex, age at randomisation, co-morbid behaviour disorder^{+}, prescription of SSRI before trial entry.
LOI	Continuous	Self-report	Baseline LOI, MFQ, ABQ scores, treatment allocation region, sex, age at randomisation, co-morbid behaviour disorder^{+}, prescription of SSRI before trial entry.
HoNOSCA	Continuous	Interview Rated	Baseline HoNOSCA ,MFQ, LOI and ABQ scores, treatment allocation, region, sex, age at randomisation, co-morbid behaviour disorder^{+}, prescription of SSRI before trial entry
ABQ	Binary	Self-report	Baseline ABQ, plus MFQ score, treatment allocation, region, sex, age at randomisation, co-morbid behaviour disorder^{+}, prescription of SSRI before trial entry.
K-SADS MDD	Binary	Interview Rated	See MFQ outcome above
MFQ ≥26	Binary	Self-report	See MFQ outcome above

SR= Self-report, IR=interviewer-rated

+ co-morbid behaviour disorder i.e., a diagnosis of oppositional defiant disorder or conduct disorder. Note, this was added as a binary variable at the analysis stage since it was found to be significantly predictive of missing data.

Trial hypotheses (see below) related to the immediate post treatment follow-up period and the long-term follow-up. The model was therefore fitted to the post treatment data (≥36 weeks) and the marginal effect of treatment was estimated at 52 weeks and 86 weeks post randomisation. At each time-point two comparisons were made; STPP against CBT and CBT and STPP against BPI. The sample size calculation used a significance level of 2.5% to allow for this multiplicity. A Bonferroni correction has not been applied to the p-values, but readers should use a 2.5% significance level to maintain the family-wise 5% level at a particular point of assessment. As well as the marginal effects, the treatment effect and time with treatment interaction are also reported with accompanying inference based on a likelihood ratio test. For all models, time was centred by subtracting the overall (grand) mean of assessment times based on the available data for the particular analysis being undertaken. This makes the intercept interpretable when there is a treatment by time interaction.

Where baseline scale covariate data was not obtained simple imputation which is based on multiple regression was used as suggested by White and Thompson (100). The following covariates were used: region, comorbid behaviour disorder (Conduct disorder and/or Oppositional defiant disorder), all anxiety disorders combined, SSRI prescription before trial entry (if missing assumed not to be prescribed) , age at randomisation, sex and baseline severity MFQ score.

The proportion of the total variance due to therapist, which can be called the intra-therapist correlation coefficient (ITCC), varies with time due to the random gradient term in the model. For comparative purposes the ITCC was calculated as:

$$\sigma_T^2 \Big/ \left(\sigma_T^2 + \sigma_P^2 + \sigma_\varepsilon^2\right)$$

where σ_T^2 is the between therapist variance, σ_P^2 is the patient level random intercept variance and σ_ε^2 is the residual error variance. This estimates the ITCC at the grand mean centred time-point.

A secondary analysis estimated the treatment effect over the treatment period based on data gathered before 36 weeks. This model did not include a time with treatment interaction since there was only the notional week 6 and 12 assessments to use as outcome data.

Analysis of the binary secondary outcome measures

The analysis of binary secondary end-points which included the ABQ, MDD and MFQ≥26 were analysed using a longitudinal GEE model with robust standard errors. This model was fitted to post treatment data (≥36 weeks) and the marginal differences in proportions were estimated for STPP vs CBT and for CBT + STPP vs BPI at weeks 36, 52 and 86.

Planned subgroup analyses

This trial included an investigation of potential moderator effects on treatment response for the primary outcome before and after thirty-six weeks. The effect of moderators was tested by adding a moderator with treatment interaction into the main effects models for treatment. The moderator measrues are described in chapter 7.

As noted in chapter 7 two moderators are considered: i) depressive thinking style ii) ruminative response style .

Hypotheses for the DEQ at baseline:

1) Elevated relatedness/dependent scores will be associated with a relatively better response in the STPP group compared to BPI or CBT groups.
2) Elevated self-critical/identity scores will be associated with a relatively better response in the CBT group compared to BPI or STPP groups.

Hypotheses for the RRS at baseline

1) Higher scores will show a better treatment response in the CBT compared to the BPI and STPP arms.

Economic evaluation method

Aim

The aim of the economic evaluation was to investigate the cost-effectiveness of psychological treatments for adolescent depression and in particular to determine whether the additional cost of the two specialised treatments, CBT and STPP, can be justified by improvements in effectiveness and/or decreased use of health and social care services compared to BPI by 86 weeks follow up.

Perspective

The a priori perspective of the economic evaluation was societal, including the use of all health, social care, education and criminal justice sector resources plus family costs in the form of travel to trial intervention sessions and productivity losses of the primary carer resulting from their child's illness. However, criminal justice and productivity losses were not found to be relevant to this population, being very low, and were excluded from the analysis.

Method of economic evaluation

The primary economic analysis was a cost-effectiveness analysis with outcomes expressed as quality adjusted life years (QALYs), as recommended by NICE (101).

Calculation of costs

The process of calculating costs was separated into the identification, measurement and valuation of relevant resources.

Identification of resources

Relevant resources were identified based on the results of previous studies in adolescent depression (11) and in discussion with study clinicians and patient representatives and resource use was collected in the following domains:

Delivery of the BPI, CBT and STPP interventions
Use of NHS secondary care services

- Inpatient stays (mental health and all medical specialties)
- Outpatient appointments (mental health and all medical specialties)
- Accident and emergency attendances

Use of NHS primary care services

- General practitioner (in surgery, at home and by telephone)
- Community nurse (for example practice nurse, district nurse, health visitor, midwife)
- Community paediatrician
- Community mental health service

- Community medical professional e.g. physiotherapist
- School based mental health and medical professionals

Use of medication in the following areas

- Antidepressants
- Sleeping tablets
- Mood stabilisers/antipsychotics

Use of social care, education and voluntary sector services

- Foster care and residential care
- Staffed accommodation such as hostel
- Social worker
- Specialist education facilities
- Education psychologist
- Family support worker
- Youth worker
- Youth offending team worker

Measurement of resources

- **Trial interventions**

The trial therapists recorded details of attendance and non-attendance at treatment sessions, and duration of treatment sessions for each study participant throughout the trial.

- **Other health, social care, education and voluntary services**

Data on use of all other services included in the study perspective were collected using the Child and Adolescent Service Use Schedule (32). The CA-SUS was developed using data from several child and adolescent mental health trials and was further modified and successfully employed in a previous trial in adolescent depression (32). The CA-SUS was completed with participants and family members in interview with a researcher at baseline and at the 6, 12, 36, 52 and 86 week follow-up interviews. At baseline, information covered the previous three months. At each of the follow-up interviews, service use since the previous interview was recorded; in this way, the entire period from baseline to final follow-up was covered. The CA-SUS asks participants for the number and duration of contacts with various services and professionals.

Valuation of resources

To calculate the total cost of the resources used by each study participant, a unit cost was applied to each resource use item. All unit costs are for the financial year 2011/12, uprated, where necessary, using the Hospital and Community Health Services Index (102) . Costs in the second year were discounted at a rate of 3.5% as recommended by NICE (101). All unit costs are summarised in Table 2.

Table 2: Unit costs applied to economic data

Service	**Unit**	**Cost (£)**
CBT	Per session	71-111
STPP	Per session	64-190
BPI	Per session	58-171
Medication	Per daily dose	various
Inpatient	Per night	495-632
Outpatient	Per appointment	30-624
Accident and Emergency	Per attendance	131-155
Ambulance	Per trip	230
GP surgery	Per minute of patient contact	3.40
GP home	Per home visit minute	4.30
GP telephone	Per minute of patient contact	3.38
Practice nurse	Per minute of face-to-face contact	0.88
District nurse, health visitor, midwife	Per home visit minute	1.03
CAMHS team	Per contact	225
Counsellor/therapist	Per minute of client contact	1.08
Social worker	Per minute	3.43
Support worker/ youth worker	Per minute	0.61
Education psychologist	Per minute	2.27

Physiotherapist	Per contact	80
Speech and language therapist	Per contact	88
Dietitian	Per contact	71
Youth offending team worker	Per minute	3.43

Trial treatments

Treatment sessions were costed on the basis of the profession and grade of the therapist that delivered each session for each trial participant, hence the range of unit costs detailed in table 2. The length of the treatment sessions was extracted from the average duration of treatment recorded in the session record forms. Average duration of sessions was 45 minutes for BPI, 50 minutes for STPP and 55 minutes for CBT. For the base case analysis, only the costs of the sessions which the young person attended were included. This assumption was employed because of an understanding that clinicians are usually able to do something else during the time freed up by missed appointments. In a sensitivity analysis, an estimate of the cost of these sessions that were offered but not attended was included. The data for this analysis came from the records held by the trial therapists and are the closest data to non-attendance available. The rate of non-attended sessions was included at 50% of the cost of a full session, which assumes professionals make some use of the time available, but not all.

Antidepressants and other medication

The total cost of antidepressants prescribed and other included medication costs were calculated using daily dose information and costs of the generic drug as listed in the British National Formulary (103).

Secondary care services

Unit costs for all hospital services were taken from the National Schedule of NHS Reference costs for 2013 and were costed on the basis of the medical specialty attended by the study participant (101).

Primary care services and social care and voluntary services

For NHS primary care services, social workers and support workers costs contained in the Unit Costs of Health and Social Care (102) and NHS Reference costs (104) were used.

Calculation of Quality Adjusted Life Years (QALYs)

QALYs were calculated using the area under the curve approach after the health states from the EQ-5D (see chapter 5 for details of method and evaluation) were converted into utility scores using responses from a representative sample of adults in the UK (60). It was assumed that changes in utility score over time followed a linear path (61) . QALYs in the second year were discounted at a rate of 3.5% as recommended by NICE (62) and all analyses were adjusted for baseline utility scores to take into consideration the impact any baseline differences will have on the area under the curve (105) .

Data analysis

For base case calculations, complete case analysis (excluding subjects with missing data) was used, with the impact of missing data explored in sensitivity analyses. All analyses were carried out on an intention to treat basis using STATA 11.1 (99).

Resource use

Resource use by study participants is reported descriptively by randomised group at 86-weeks as mean use for the group as a whole and percentage of the group ~~who had at least one~~in contact with that service. No statistical comparisons between use of services are made to avoid problems associated with multiple testing, and because the focus of the economic evaluation is on cost and cost-effectiveness.

Difference in costs and QALYs

A number of tests for differences in costs at 86 weeks between randomised groups were completed:

1) CBT v BPI
2) STPP v BPI
3) CBT v STPP

These were analysed using linear regression models with the following pre-specified covariates: baseline costs (total cost over the previous 3 months), region (East Anglia, North London, North West), behavioural disorder at baseline (measured using the K-SADS-PL) and antidepressant use at baseline. The validity of the results were confirmed using bias-corrected, non-parametric bootstrapping (repeat re-sampling) (106). Despite the

skewed nature of cost data, this approach is recommended to enable inferences to be made about the arithmetic mean (107).

Cost-effectiveness analyses

For the cost-effectiveness, analysis moves from considering differences in costs and outcomes in terms of statistical significance to analysing costs and outcomes together in a decision-making context. The cost-effectiveness analysis, undertaken using QALYs calculated from the EQ-5D measure of health-related quality of life, was completed for the following comparisons:

1) CBT v BPI
2) STPP v BPI
3) CBT v STPP
4) CBT v STPP v BPI

Initially, incremental cost-effectiveness ratios (ICERS) were calculated, which are the difference in mean cost divided by the difference in mean effect (108). Because ICERs are calculated from four sample means and are therefore subject to statistical uncertainty, 5000 re-samples (bootstrapping) from the cost and outcomes data were used to generate a distribution of mean costs and effects (109). These distributions were plotted onto the cost-effectiveness plane for interpretation. Replications that fall in the South-West quadrant of the plane suggest that the intervention is less costly and less effective than the comparator and those that fall in the South-East quadrant suggest that the intervention is less costly and more effective than the comparator. Replications in the North-West quadrant suggest the intervention is more costly and less effective than the comparator, while those in the North-East quadrant suggest the intervention is more costly and more effective than the comparator.

The bootstrapped distributions were also used to calculate the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (the ceiling ratio, λ) that a decision-maker might be willing to pay for a unit improvement in outcome. To explore the uncertainty that exists around estimates of mean costs and effects as a result of sampling variation and uncertainty regarding the maximum value of λ, cost-effectiveness acceptability curves (CEACs) are presented by plotting these probabilities for a range of possible values of the ceiling ratio (λ) (110). All analyses used baseline costs, region and behavioural disorder at baseline as covariates.

Sensitivity analyses

A number of sensitivity analyses were carried out to test the robustness of the assumptions made:

1. The cost of sessions offered but not attended was explored by increasing the cost from the assumption of zero applied in the main analysis (which assumes professionals are able to make use of the time available to undertake alternative tasks) to 50% of the cost of a session (which assumes professionals make some use of the time available, but not all). Data were calculated as the number of sessions offered minus the number of sessions attended, which may not be exactly equivalent to the number of DNAs (did not attend) as sessions may have been offered but cancelled or rearranged. This analysis should therefore be interpreted with caution.
2. The impact of missing data was considered using multiple imputation of missing values.
3. Due to the variation in the timing of follow-up, cost per week was calculated and analysed.

Chapter 9

Clinical Results

This chapter reports the characteristics of young people entering the trial (9.1), the details of trial therapies and medication received (9.2), the analysis of clinical outcomes (9.3) , moderator analyses (9.4) and summarizes data on adverse events (9.5). For clarity of exposition some results are given in an appendix at the end of this chapter.

9.1 Characteristics of young people entering the trial

A total of 557 participants had baseline assessments. Of these 87 were excluded from the study (see consort diagram Figure 2 for reasons for exclusion). The remaining 470 participants were randomised of which 5 later withdrew consent (3 BPI, 1 CBT and 1 STPP). Amongst the remaining 465 participants, 155, 154 and 156 were randomised to BPI, CBT and STPP, respectively. The East Anglia regional centre recruited the largest number of participants (40%, n=185) followed by the North West (33%, n=153) with North London recruiting the smallest (27%, n=127). Recruitment was from 5 CAMHS clinics each in East Anglia and North London, and from 6 in the North West.

Table 3 summarize the demographic and clinical characteristics of the three randomised groups at entry into the trial. The mean age of the sample was 15.6 (SD 1.4). A total of 348 (75%) were female and 85% (382/450) were white. Based on those with SSRI prescription information, 20% were prescribed a SSRI prior to entry into the trial. The baseline characteristics of each treatment group are presented in Table 3. There were no marked differences between treatment groups. Note, that baseline values of outcome measures are tabulated with the summaries of follow-up data in Table 12, section 9.3.

Table 3: Characteristics of participants at baseline: frequency (%) of participants are presented unless stated otherwise.

	BPI (n=155) Freq. (%)	CBT (n=154) Freq. (%)	STPP (n=156) Freq. (%)
Female	115 (74)	114 (74)	119 (76)
Age in Year at entry	15.6 (1.4)[a]	15.6 (1.4)[a]	15.6 (1.5)[a]
White*	121 (82)	131 (86)	130 (86)
Regional centre			
East Anglia	61 (39)	62 (40)	62 (40)
North London	43 (28)	41 (27)	43 (27)
North West	51 (33)	51 (33)	51 (33)
SSRI prescribed before trial entry[+]	29 (19)	32 (21)	28 (18)
Behavioural disorder	20 (13)	20 (13)	16 (10)
Number of			
Depressive Symptoms	8.4 (2.5)[a]	8.7 (2.3)[a]	8.3 (2.5)[a]

*excludes n=15 where ethnic group/origin was not stated or missing

+excludes n=9 with missing information

[a]Mean (SD)

Table 4 gives the prevalence of concurrent depressive symptoms from the K-SADS-PL. The most prevalent symptom was sleep disturbance (92%) followed by depressed mood (84%). The mean number of symptoms was 8.4 for the BPI group; 8.7 for CBT and 8.3 for STPP (see Table 3 above). Recent suicide attempts refer current major depression episode. Lifetime suicide attempts refer to all lifetime except current episode.

Table 5 gives a detailed breakdown of co-morbid psychiatric diagnoses recorded in the baseline K-SADS-PL by treatment group. A total of 225 (48%) were concurrently comorbid for at least one other psychiatric disorder. Of these 134 (29%) and 60 (13%) had one and two comorbidities, respectively. The maximum number of comorbidities was 5 in the BPI group and 4 in the other two groups. Overall, the most frequent comorbid diagnoses were generalised anxiety disorder and social phobia. There were no marked differences between the three treatment groups in these characteristics.

Table 4: Depressive symptoms recorded at baseline research assessment

Depressive Symptom	BPI (n=155) Freq.	(%)	CBT (n=154) Freq.	(%)	STPP (n=156) Freq.	(%)	Total (N=465) Freq.	(%)
Two Weeks Prior to Baseline Assessment								
Sleep disturbance	141	(91.0)	141	(91.6)	145	(92.9)	427	(91.8)
Depressed Mood	131	(84.5)	134	(87.0)	125	(80.1)	390	(83.9)
Disturbed Concentration, inattention	112	(72.3)	119	(77.3)	118	(75.6)	349	(75.1)
Fatigue, lack energy	117	(75.5)	113	(73.4)	111	(71.2)	341	(73.3)
Worthlessness	108	(69.7)	101	(65.6)	105	(67.3)	314	(67.5)
Anhedonia, apathy	96	(61.9)	104	(67.5)	103	(66.0)	303	(65.2)
Irritable, anger	97	(62.6)	104	(67.5)	91	(58.3)	292	(62.8)
Suicidal Ideation	95	(61.3)	91	(59.1)	97	(62.2)	283	(60.9)
Decreased Appetite	71	(45.8)	78	(50.6)	71	(45.5)	220	(47.3)
Hopelessness	74	(47.7)	66	(42.9)	71	(45.5)	211	(45.4)
Indecision	47	(30.3)	62	(40.3)	51	(32.7)	160	(34.4)
Guilt	53	(34.2)	51	(33.1)	45	(28.8)	149	(32.0)
Agitation	43	(27.7)	53	(34.4)	50	(32.1)	146	(31.4)
Psychomotor retardation	37	(23.9)	38	(24.7)	36	(23.1)	111	(23.9)
Weight loss	29	(18.7)	25	(16.2)	23	(14.7)	77	(16.6)
Increased appetite	21	(13.5)	23	(14.9)	23	(14.7)	67	(14.4)
Weight gain	15	(9.7)	12	(7.8)	15	(9.6)	42	(9.0)
Hallucinations	12	(7.7)	16	(10.4)	6	(3.8)	34	(7.3)
Delusions	4	(2.6)	5	(3.2)	5	(3.2)	14	(3.0)
Recent Suicidal Attempt	3	(1.9)	2	(1.3)	7	(4.5)	12	(2.6)
Lifetime Suicidal Attempt	57	(36.8)	48	(31.2)	55	(35.3)	160	(34.4)

Table 5: Co-morbidity at baseline research assessment

Comorbid diagnosis	BPI (n=155)		CBT (n=154)		STPP (n=156)		Total (n=465)	
	Freq.	(%)	Freq.	(%)	Freq.	(%)	Freq.	(%)
Generalised anxiety disorder	34	(21.9)	34	(22.1)	31	(19.9)	99	(21.3)
Social Phobia	19	(12.3)	20	(13.0)	22	(14.1)	61	(13.1)
Oppositional defiant disorder	14	(9.0)	18	(11.7)	12	(7.7)	44	(9.5)
Specific phobia	16	(10.3)	13	(8.4)	6	(3.8)	35	(7.5)
Post-traumatic stress disorder	6	(3.9)	12	(7.8)	14	(9.0)	32	(6.9)
Separation anxiety disorder	6	(3.9)	9	(5.8)	5	(3.2)	20	(4.3)
Conduct disorder	7	(4.5)	2	(1.3)	5	(3.2)	14	(3.0)
Obsessive compulsive disorder	2	(1.3)	5	(3.2)	3	(1.9)	10	(2.2)
Panic without Agoraphobia	2	(1.3)	3	(1.9)	2	(1.3)	7	(1.5)
Agoraphobia	3	(1.9)	1	(0.6)	3	(1.9)	7	(1.5)
Alcohol abuse	2	(1.3)	2	(1.3)	2	(1.3)	6	(1.3)
Panic with Agoraphobia	2	(1.3)	1	(0.6)	2	(1.3)	5	(1.1)
Attention deficit hyperactivity disorder	2	(1.3)	1	(0.6)	1	(0.6)	4	(0.9)
Bulimia nervosa	0	(0)	1	(0.6)	2	(1.3)	3	(0.6)
Substance abuse	3	(1.9)	0	(0)	0	(0.0)	3	(0.6)
Anorexia nervosa	0	(0)	0	(0)	2	(1.3)	2	(0.4)
Substance dependence	1	(0.6)	0	(0)	1	(0.6)	2	(0.4)
Enuresis	1	(0.6)	0	(0)	1	(0.6)	2	(0.4)
Alcohol dependence	0	(0)	0	(0)	1	(0.6)	1	(0.2)
Encopresis	0	(0)	0	(0)	0	(0)	0	(0)

Non-suicidal self injury

Recent NSSI, during the current depression episode was reported by 85 (18.3%) of the patients and lifetime NSSI by 246 (52.9%). The frequency for the treatment groups for recent NSSI was BPI (26,16.8%), CBT (25, 16.2%), STPP (34,21.8%). The frequency for the treatment groups for lifetime NSSI was BPI (87,56.1%), CBT (75, 48.7%), STPP (84, 53.9%)

9.2 Trial treatments and medication

Uptake and duration of trial therapies

The numbers of patients recorded as having started trial therapy were 138 (89%) for BPI, 133 (86%) for CBT, and 133 (85%) for STTP. Due to differences in organisation and type of service the time from randomisation to start of therapy could vary between treatments and regional centres. Figure 3 displays the time from randomisation until the start of therapy for the three trial interventions as a Kaplan-Meier plot. The longest time until the start of therapy was 36 weeks, which was for CBT. Forty-seven young people did not start therapy and are censored at the longest recorded start time. When a Cox proportional hazards model was fitted to the time until start of therapy with covariates including trial therapy and region there was evidence of an interaction between region and trial therapy. Table 6 gives the median time to start of therapy by treatment and region, from which it is apparent that time until the start of BPI was rather shorter in North London than other sites, and that time until the start of CBT was rather longer in East Anglia than others.

Figure 3: Time from randomisation to start of trial therapy by group

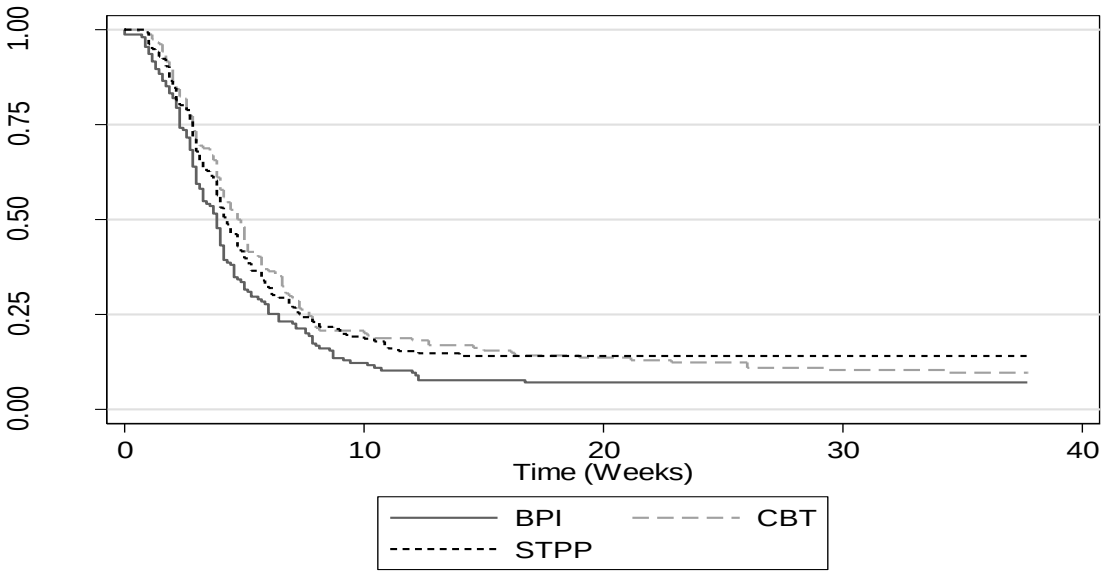


Table 6 displays the median and mean number of sessions attended by participants in each treatment arm.

Table 6: Estimated median time (95% confidence interval) in weeks to start of therapy by trial therapy group and region

	BPI		CBT		STPP	
Region	Median	(95% c.i.)	Median	(95% c.i.)	Median	(95% CI)
East Anglia	4.3	(3.3 to 5.6)	7.3	(5.1 to 10.1)	4.7	(3.9 to 5.7)
North London	2.9	(2.0 to 3.7)	4.0	(3.0 to 4.7)	3.9	(2.7 to 4.4)
North West	4.0	(3.1 to 4.6)	4.0	(2.9 to 4.9)	4.4	(3.1 to 6.1)

Each of the three trial therapies recommended a number of treatment sessions (see chapter 5). The number specified for each of the three trial interventions were 12 for BPI, 20 for CBT and 28 for STPP. Table 7 gives the number of clinical sessions attended by young people. Of those patients randomised to BPI 17% (24/138) had more than the suggested 12 sessions. Of those randomised to CBT 3% (5/133) had more than the recommended 20 sessions, and for those randomised to STTP 2% (3/133) had more than the recommended 28 sessions. Table 7 also gives summary statistics for numbers of sessions received. Amongst patients that received therapy, patients randomised to BPI had fewer sessions (Kruskal Wallis $p<0.001$) and the median number of treatment sessions attended were 6 for BPI, and 8 for CBT and STTP respectively. Less than half of all patients that received their randomised treatment attended more than half of the recommended number of sessions for that treatment modality.

A clinical estimate of adherence to therapy for each therapeutic modality was mad by the lead clinical specialists for each trial treatment. As there is no prior scientific evidence these operational definitions of minimum sufficient attendance were ‘best practise based’ and cannot therefore index a formal required therapeutic dose. They are given here for descriptive purposes only but may be hypothesis forming for future reference.

Clinical adherence that might result in some therapeutic gain was defined by the lead therapeutic specialists in consultation with therapists in each treatment arm. The investigators agreed to set 2 sessions for BPI and 5 sessions for CBT and STPP respectively as the minimum number of sessions likely to result in therapeutic gain. The proportion of patients in each treatment group attending what is estimated as inadequate or adequate

number of sessions for putative clinical adherence is shown in Table 6. Conditional on attending at least one session, 17% (24/138) exceeded the proscribed maximum number of sessions on BPI, compared to 4% (5/133) for CBT and 2%(3/133) for STPP. The number (%) of sessions attended by treatment allocation (with the adherence thresholds defined by doted lines) are shown in Table 7.

Table 7: Number (%) of sessions attended by treatment allocation

Number of sessions	BPI Freq.	BPI (%)	BPI (%≥)[a]	CBT Freq.	CBT (%)	CBT (%≥)[a]	STPP Freq.	STPP %	STPP (%≥)[a]	
Missing	6	(3.9)		6	(3.9)		2	(1.3)		
0	11	(7.1)	-	15	(9.7)	-	21	(13.5)	-	
1	12	(7.7)	(92.6)	11	(7.1)	(89.9)	8	(5.1)	(86.4)	Below Adherent
2	13	(8.4)	(84.6)	8	(5.2)	(82.4)	9	(5.8)	(81.2)	
3	9	(5.8)	(75.8)	4	(2.6)	(77.0)	4	(2.6)	(75.3)	
4	15	(9.7)	(69.8)	6	(3.9)	(74.3)	6	(3.8)	(72.7)	
5	9	(5.8)	(59.7)	10	(6.5)	(70.3)	8	(5.1)	(68.8)	
6	12	(7.7)	(53.7)	11	(7.1)	(63.5)	5	(3.2)	(63.6)	Adherent
7	10	(6.5)	(45.6)	6	(3.9)	(56.1)	4	(2.6)	(60.4)	
8	4	(2.6)	(38.9)	8	(5.2)	(52.0)	13	(8.3)	(57.8)	
9	8	(5.2)	(36.2)	5	(3.2)	(46.6)	1	(0.6)	(49.4)	
10	6	(3.9)	(30.9)	6	(3.9)	(43.2)	3	(1.9)	(48.7)	
11	7	(4.5)	(26.8)	7	(4.5)	(39.2)	6	(3.8)	(46.8)	
12	9	(5.8)	(22.1)	5	(3.2)	(34.5)	2	(1.3)	(42.9)	
13	3	(1.9)	(16.1)	7	(4.5)	(31.1)	6	(3.8)	(41.6)	
14	5	(3.2)	(14.1)	8	(5.2)	(26.4)	2	(1.3)	(37.7)	
15	3	(1.9)	(10.7)	2	(1.3)	(20.9)	3	(1.9)	(36.4)	
16	2	(1.3)	(8.7)	4	(2.6)	(19.6)	2	(1.3)	(34.4)	
17	1	(0.6)	(7.4)	7	(4.5)	(16.9)	1	(0.6)	(33.1)	
18	4	(2.6)	(6.7)	2	(1.3)	(12.2)			(32.5)	
19	1	(0.6)	(4.0)	3	(1.9)	(10.8)	5	(3.2)	(32.5)	
20	1	(0.6)	(3.4)	8	(5.2)	(8.8)	3	(1.9)	(29.2)	
21	1	(0.6)	(2.7)	3	(1.9)	(3.4)	4	(2.6)	(27.3)	
22			(2.0)	1	(0.6)	(1.4)	4	(2.6)	(24.7)	
23	1	(0.6)	(2.0)			(0.7)	5	(3.2)	(22.1)	
24			(1.3)	1	(0.6)	(0.7)	5	(3.2)	(18.8)	
25			(1.3)			(0.0)	7	(4.5)	(15.6)	
26			(1.3)			(0.0)	4	(2.6)	(11.0)	
27			(1.3)			(0.0)	4	(2.6)	(8.4)	
28			(1.3)			(0.0)	6	(3.8)	(5.8)	
29			(1.3)			(0.0)	1	(0.6)	(1.9)	
33	1	(0.6)	(1.3)			(0.0)			(1.3)	
39			(0.7)			(0.0)	1	(0.6)	(1.3)	
42			(0.7)			(0.0)	1	(0.6)	(0.6)	
43	1	(0.6)	(0.7)			(0.0)			(0.0)	
Total	155	100		154	100		156	(100.0)		
Mean (SD)	7.3	(6.4)		8.8	(6.5)		11.8	(10.0)		
Median	6			8			8			

[a] Calculated where the number of sessions are known i.e., excluding missing category.

Figure 4 displays the duration of trial therapy for those young people with a recorded start and completion date by treatment group. It was assumed that the duration of therapy was one day for young people attending just one therapy session. Summary statistics for the same data are given in Table 8. Average duration of therapy were quite similar and not significantly different (Kruskal Wallis p= 0.238). The median duration of therapy was however greater for STPP (30.1 weeks) than for either BPI (22.1 weeks) or CBT (23.1) , which can be seen in Figure 4. There is no noticeably greater variation in the length of therapy for BPI (sd=21.5) than for CBT (s.d.= 17.7) and STPP (s.d.= 16.8), which can be explained by rather more patients exceeding the suggested number of sessions for BPI (see Table 7).

Figure 4: Duration of trial therapy by treatment group

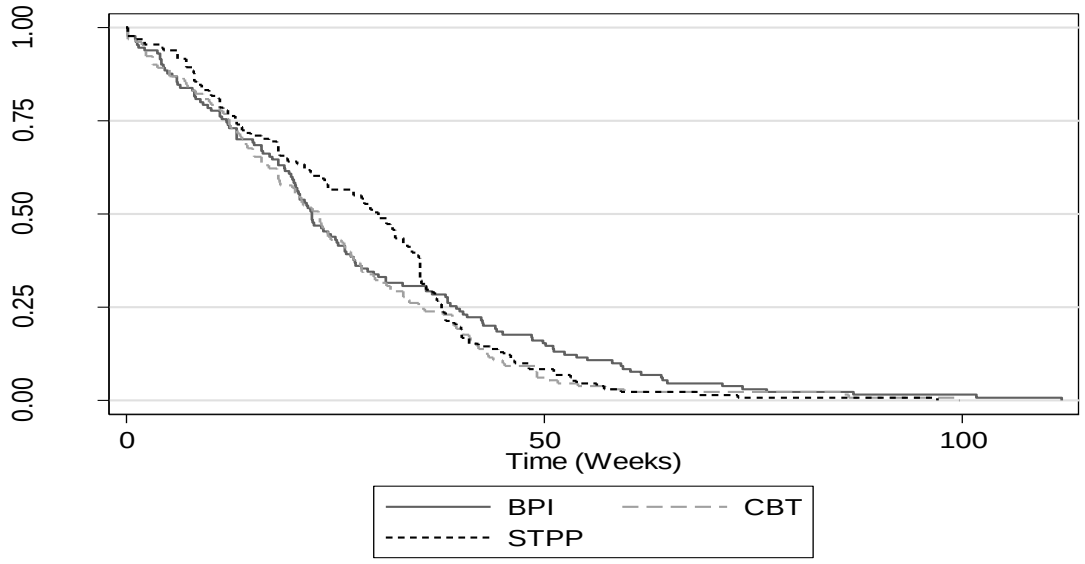


Table 8: Summary statistics for duration of therapy (weeks from first to last session)

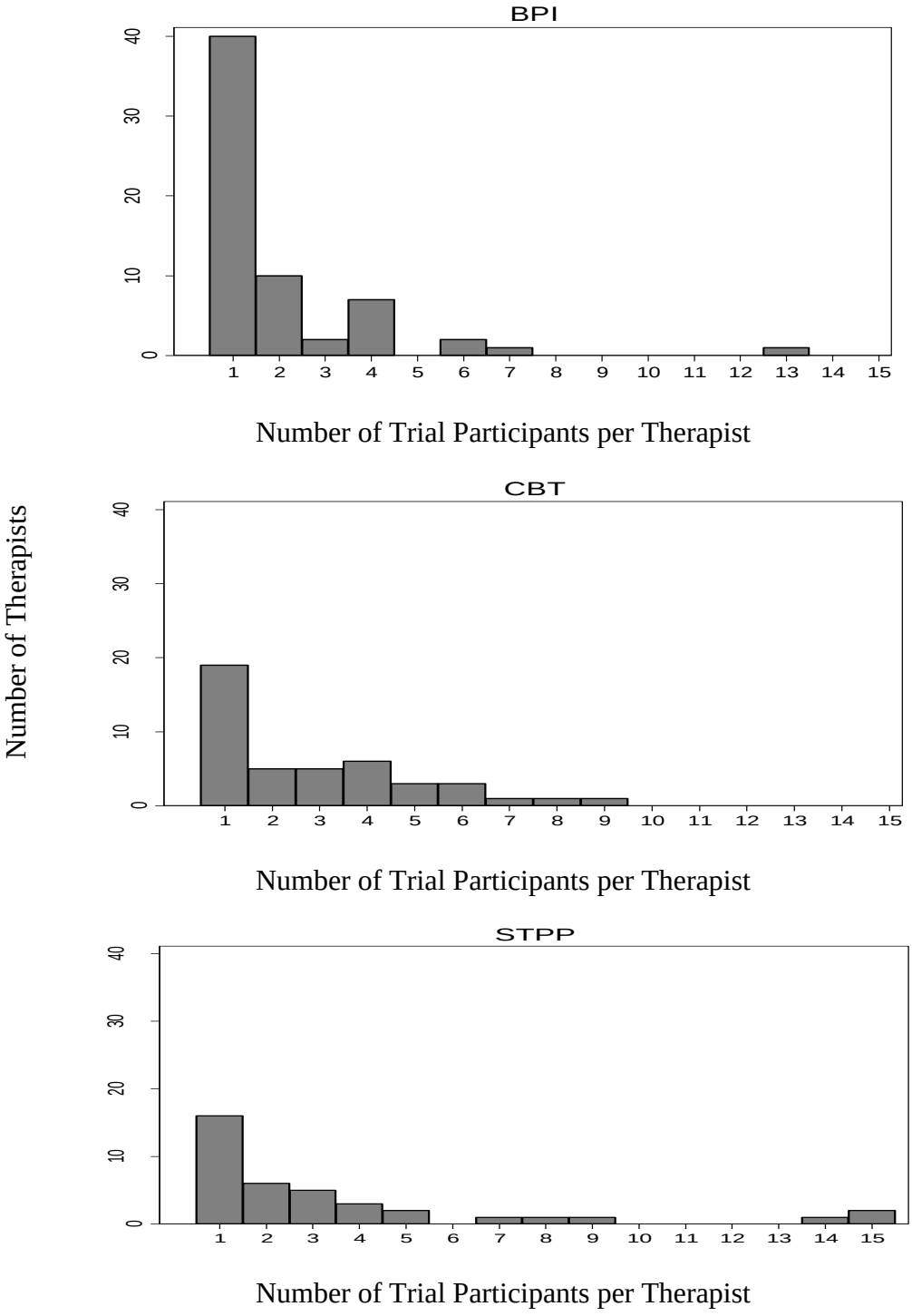
Treatment	Med	Max	Mean	SD	N
BPI	22.1	111.9	27.5	21.5	130
CBT	23.1	99.6	24.9	17.7	130
STPP	30.1	97.0	27.9	16.8	131

Note, the minimum duration was one day.

All therapists delivering a trial therapy were given a trial therapist identifier. For young people receiving trial treatments the therapist identifier was missing for 18 (%) BPI trial treatments, for 13 (%) CBT and for 2 (%) STPP. A total of 63 therapists delivered BPI, 44 delivered CBT and 38 STPP. For all three modalities the young person received their trial therapy from a single trial therapist. Figure 5 gives the distribution of the number of young people treated by each therapist for each treatment arm. The number of trial participants seen

by a particular therapist ranged from 1 to a maximum of 15. Forty BPI therapists treated only one young person in the trial whereas the corresponding figures for CBT and STPP were 19 and 18 respectively, which can be explained in part by the rather larger number of available BPI compared to CBT or STPP therapists.

Figure 5: Frequency distribution of number of trial participants seen by a trial therapist for each therapy modality



Adherence and differentiation of trial therapies

Treatment adherence

Each tape was rated twice by two separate raters using the CPPS and the mean of the two scores taken as the rating for a tape . Table 9 summarizes the ratings on the Cognitive Behavioural (CB) and Psychodynamic-Interpersonal (PI) sub-scales. Based on the CPPS ratings, 74% of the CBT sessions (56/76) had a score of 2 or above ('somewhat characteristic') on the CB sub-scale, and can therefore be considered adherent to the CBT treatment protocol. 80% of the STPP sessions (65/81) where 2 or above on the PI sub-scale, and can therefore be considered to be adherent to the STPP protocol.

Based on the BPI-S ratings, 81.3% of the BPI sessions (61/75) were rated as 2 or above on 2 out of 3 'core' items and 4 out of 8 items in total, and can therefore be considered to be adherent to the BPI protocol.
It should be kept in mind that the CPPS and BPI adherence measures are not directly comparable, as each scale has its own criteria for assessing what signifies an 'adherent' treatment. Therefore the results give an opportunity to compare levels of adherence between STPP and CBT, but not a direct statistical comparison of the magnitude of adherence between all three treatment arms.

Table 9: CPPS sub-scale score by treatment arm

	CB sub-scale							*PI sub-scale*						
	≥2	*(%)*	*mean*	*SD*	*median*	*p25*	*p75*	*≥2*	*(%)*	*mean*	*SD*	*median*	*p25*	*p75*	*n*
BPI	*21*	*(28.0)*	*1.55*	*0.71*	*1.35*	*1*	*2.1*	*14*	*(18.7)*	*1.37*	*0.65*	*1.25*	*0.85*	*1.85*	*75*
CBT	*56*	*(73.7)*	*2.49*	*0.91*	*2.43*	*1.83*	*3*	*15*	*(19.7)*	*1.48*	*0.69*	*1.4*	*0.98*	*1.83*	*76*
STPP	*0*	*(0)*	*0.55*	*0.37*	*0.45*	*0.3*	*0.7*	*65*	*(80.2)*	*2.64*	*0.8*	*2.65*	*2.05*	*3.3*	*81*

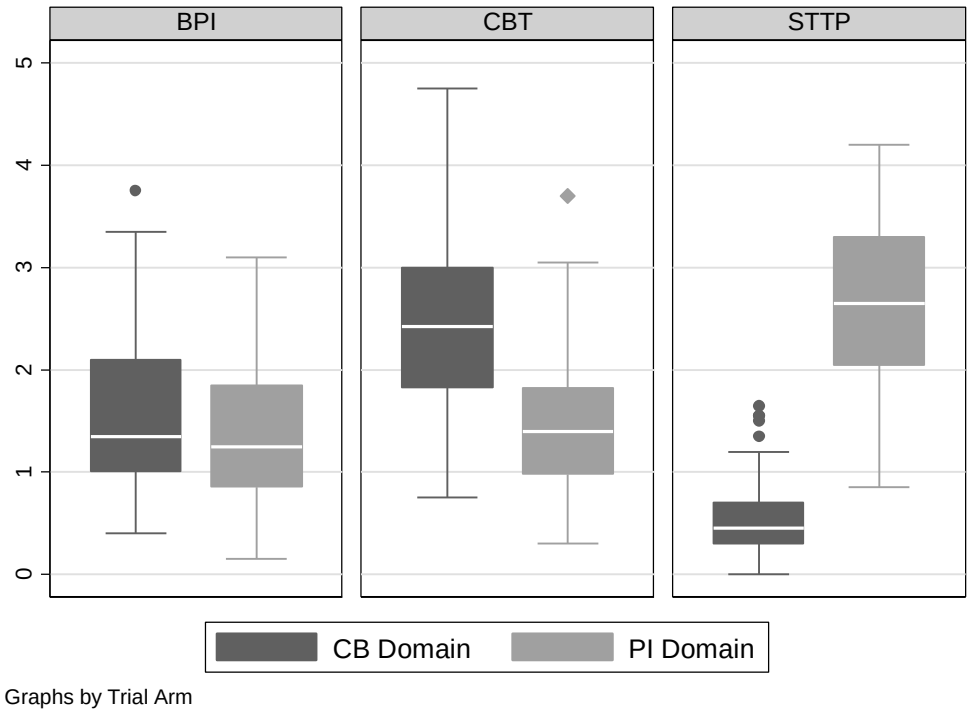
Key: p25, 25th percentile; p75, 75th percentile

Treatment differentiation

Table 12, below, gives the mean ratings for each of the three treatment arms on the CPPS sub-scales (psychodynamic-interpersonal and cognitive-behavioural), showing the proportion of techniques associated with the other treatment arm that was used by BPI, CBT and STPP respectively.
Figure 6 gives a box-plot for the treatment differentiation score for each domain of the CPPS for the three treatments, and corresponding summary statistics are given in Table 12. This shows that all three treatment arms were significantly differentiated, based on blind double-ratings of the CPPS. The mean cognitive-behavioural (CB) sub-scale score was 1.91 higher for CBT than STPP (95% CI 1.73 to 2.09,p <0.0001). The

mean psychodynamic-interpersonal (PI) sub-scale score was 1.18 higher for STPP than CBT (95% CI 1.01 to 1.3,p <0.0001). BPI had a significantly lower CB sub-scale mean than CBT (mean diff. = -0.93, 95% CI -1.12 to - 0.75, p<0.0001) and a significantly lower PI sub-scale mean than STPP (mean diff. =-1.30, 95% CI -1.48 to -1.11, p<0.0001). In conclusion, ratings of the two CPPS sub-scales suggested that all three treatments were well differentiated.

Figure 6: Treatment differentiation based on the CPPS



Conclusion of the treatment adherence and differentiation analysis

This analysis, based on the blind, double-ratings of 232 tapes, stratified by modality and timing, aimed to evaluate treatment adherence and differentiation within the study. Dennhag et al., (2012), in a review of studies assessing treatment adherence and/or competence in psychotherapy, identify a total of 27 studies, in which a mean number of 91 tapes were rated per study (range: 16 to 615), making this analysis one of the largest studies of its kinds in psychotherapy.

Adherence ratings were conducted with good (for CPPS) to moderate (for BPI-S) intra-class correlations scores. Overall there was a relatively high level of protocol adherence by the therapists in each arm of the

study, with 81.3% of sessions meeting the threshold of adherence for BPI, compared to 80% for STPP and 74% for CBT. Previous studies (e.g. ADAPT) have reported mean scores for therapist adherence and/or competence, but have not used pre-defined cut-off scores for adherence. Direct comparisons between the figures for BPI and the two specialist psychological therapy should be interpreted with caution, however, given that BPI sessions were assessed using a different measure to the CBT and STPP treatment arms. Unlike the CBT and STPP sessions, BPI sessions were not rated blindly for treatment adherence, and had lower levels of inter-rater reliability, so findings regarding levels of adherence to BPI must be interpreted with some caution.
In addition to demonstrating good levels of protocol adherence, treatment differentiation was established between all three treatment arms. In line with our hypotheses regarding ratings on the CPPS, CBT sessions were significantly lower than STPP on the PI sub-scale; STPP sessions were significantly lower than CBT on the CB sub-scale; and BPI sessions were significantly lower than both STPP on the PI sub-scale and CBT on the CB sub-scale. This demonstrates that STPP and CBT sessions were significantly differentiated from each other, and BPI sessions were significantly differentiated from both CBT and STPP.

Antidepressant medication

Prior to randomisation 89 (19%) young people were receiving SSRI medication (Table 3). Table 10 shows the number and percentage of participants who were prescribed any antidepressant during treatment and follow-up by arm based on data provided by the health economic schedule CA-SUS. Receipt of antidepressant medication during treatment is a potential mediator of the outcome of psychological treatment. From Table 10 it would appear that a similar proportion of young people in each arm were prescribed medication during the trial treatment period (<36 weeks) suggesting that receipt of medication was independent of random allocation. There is therefore no reason to believe that medication during the therapy period would bias estimates of the treatment effect immediately post therapy unless drug therapy interacted with therapeutic modality.

During follow-up the proportion receiving any antidepressant medication increased from 27% in the treatment period to 34% for CBT, 35% for STPP and to 40% for BPI, although this difference between arms was not statistically significant (χ_2^2=0.584).

Table 10: Antidepressants (AD) prescribing during treatment and follow-up

	BPI		CBT		STTP	
<36 weeks	(n=122)		(n=120)		(n=122)	
Medication	Freq.	%	Freq.	%	Freq.	%
Citalopram	3	2.5	5	4.2	3	2.5
Fluoxetine	29	23.8	27	22.5	23	18.9
Sertraline	3	2.5	3	2.5	9	7.4
Any AD	34	27.9%	33	27.5%	32	26.2%
Not receiving medication	88	72.1	87	72.5	90	73.8
≥36 weeks	(n=125)		(n=125)		(n=124)	
Medication	Freq.	%	Freq.	%	Freq.	%
Citalopram	9	7.2	9	7.2	6	4.8
Fluoxetine	36	28.8	30	24.0	24	19.4
Sertraline	12	9.6	5	4.0	13	10.5
Any AD	50	40.0	43	34.4	43	34.7
Not receiving medication	75	60.0	82	65.6	81	65.3
All Followup	(n=137)		(n=137)		(n=137)	
Any AD	56	40.9	55	40.1	50	36.5
Not receiving medication	81	59.1	82	59.9	87	63.5

9.3 Assessment clinical outcome

Table 11 gives the response rate for the primary outcome measure (MFQ) for each assessment. A total of 16 (10%), 12 (8%) and 17 (11%) on the BPI, CBT and STPP groups respectively, had no follow-up MFQ. The CBT group had the highest response rate of 80% at the 86 week assessment. To investigate baseline characteristics that might influence non-response a logistic generalised estimating equations (GEE) model was fitted to an indicator variable of missing primary outcome data at each assessment (6 to 86 weeks) including the following covariates: randomisation, assessment number, age at randomisation, gender, region (East Anglia, North London, North West England), baseline MFQ score, SSRI prescription before trial entry, behaviour disorder (a diagnosis of ODD or CD), all anxiety disorders combined and a time by treatment by assessment interaction to investigate differential non-response. Two factors appeared to influence non-response: i) regional centre with a higher response rate in the North West regional centre (p=0.02) compared to East Anglia, ii) behaviour disorders at baseline with a lower response rate for subjects with conduct or oppositional defiant disorder (p=0.004). Behavioural disorder was not in the original list of pre-specified baseline covariates, and so was added to all models to support the *missing at random (MAR)* assumption for missing outcome data.

Table 11: Response rates and time from randomisation for the primary outcome (MFQ) by assessments.

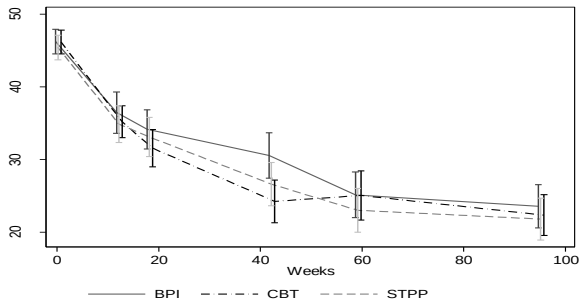
Assessment Number (week)	BPI				CBT				STPP			
	response rate		*Time since Randomisation*		*response rate*		*Time since randomisation*		*response rate*		*Time since randomisation*	
	Freq.	*(%)*	*mean*	*(Min ,Max)*	*Freq.*	*(%)*	*mean*	*(Min ,Max)*	*Freq.*	*(%)*	*mean*	*(Min ,Max)*
Baseline	155	(100)			154	(100)			156	(100)		
1 (6)	99	(64)	11.0	(6,25)	104	(68)	12.3	(7,41)	107	(69)	11.1	(6,21)
2 (12)	112	(72)	17.6	(12,33)	106	(69)	19.0	(11,38)	108	(69)	17.6	(12,28)
3 (36)	105	(68)	42.3	(36,54)	104	(68)	42.9	(35,63)	109	(70)	41.5	(31,52)
4 (52)	105	(68)	59.2	(51,76)	111	(72)	60.3	(48,92)	110	(71)	59.3	(50,85)
5 (86)	116	(75)	95.4	(73,132)	123	(80)	94.9	(82,147)	114	(73)	95.1	(69,149)

Table 12 gives summary statistics for the primary outcome measure MFQ and the secondary quantitative outcomes, which include Revised Childrens's Manifest Anxiety Scale (RCMAS), Leyton Obsessional Inventory (LOI) and Antisocial Behaviour Questionnaire (ABQ), that are self-completed questionnaires, which together with the MFQ form the YPQ, and Health of the Nation Outcome Scale for Children and Participants (HoNOSCA) that is interviewer rated.

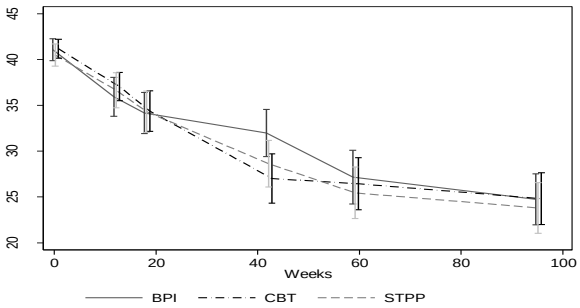
On initial inspection of the data it was clear that the ABQ was highly skewed with the standard deviation larger than the mean at many time-points and medians of zero at weeks 52 and 86 for each group. Because of the substantial skewness the decision was made to dichotomize this scale and compare the proportion of none zero scores. Further analysis of this scale is therefore presented with other binary outcomes measures below.

In Figure 7 below the mean scores with 95% confidence intervals are plotted against time since randomisation for the quantitative outcome measures. For all scales lower scores represent a better outcome, hence a greater reduction in one treatment than another represents a beneficial effect. For all four measures the profile of CBT and STPP is below that for BPI post randomisation across time-points.

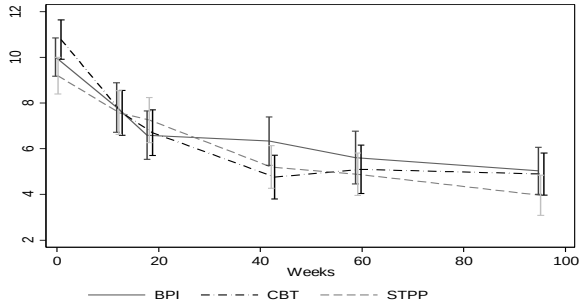
Figure 7: Mean outcome by treatment group (95% c.i.)



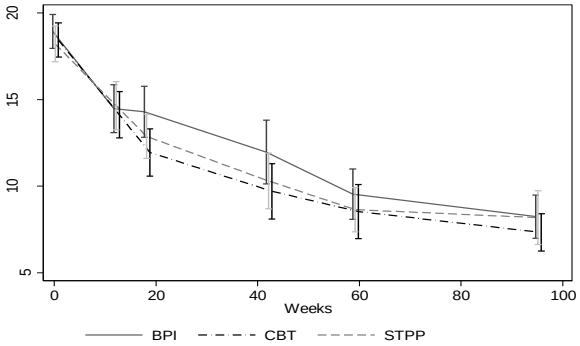
MFQ



RCMAS



LOI



HoNOSCA

Table 12: Comparison of groups for primary and secondary outcome measures

Outcome	BPI (N=155)						CBT (N=154)						STPP (N=156)					
measure	Mean	SD	Med	Min	Max	n	Mean	SD	Med	Min	Max	n	Mean	SD	Med	Min	Max	n
Primary																		
MFQ																		
Baseline	46.2	10.6	47	15	64	155	46.2	10.3	47	20	65	154	45.4	10.8	46	13	64	156
1	36.5	14.3	39	2	64	99	35.2	11.3	34.5	10	59	104	34.9	13.2	34	2	61	107
2	34.1	14.4	36	1	61	112	31.6	13.3	33	1	59	106	33.1	14.2	35.1	1	58	108
3	30.5	16.1	31	0	61	105	24.2	15.1	22.5	0	61	104	26.6	15.7	24	0	59	109
4	25.1	16.2	22.7	0	63	105	25.0	18.0	20.6	0	62	111	23.0	15.9	20	0	62.3	110
5	23.6	16.2	20.5	0	63	116	22.3	15.7	19	0	63	123	21.8	15.5	18.5	0	61	114
Secondary																		
RCMAS																		
Baseline	41.1	7.6	42	17	54	155	41.2	6.4	41	15	55	154	40.5	7.7	41.5l	8	56	155
1	35.9	10.6	38.7	0	52	98	37.1	7.9	38.4	12	53	103	36.7	10.0	39	0	56	107
2	34.2	11.9	36.6	3	56	110	34.4	11.4	37	2	56	105	34.3	11.9	37	0	54	108
3	32.0	13.3	36	0	53	104	27.0	13.7	28	2	49	102	28.6	13.3	30	0	49	107
4	27.2	14.8	29	0	50	100	26.4	14.9	28	0	56	108	25.5	14.5	26.5	0	53	104
5	24.7	14.7	26	0	53	109	24.8	15.4	27	0	56	115	23.8	14.6	26.0	0	56	108
LOI																		
Baseline	10.0	5.3	9.9	0	22	155	10.8	5.4	10	0	22	152	9.2	5.0	8.9	0	22	154
1	7.8	5.4	7	0	22	98	7.6	5.0	7	0	22	102	7.6	5.0	6	0	21	107
2	6.6	5.6	5	0	22	111	6.7	5.2	6	0	22	104	7.3	5.1	7	0	22	107
3	6.3	5.4	5	0	19	103	4.8	4.8	4	0	21	101	5.2	4.9	4	0	21	107
4	5.6	5.8	4	0	22	99	5.1	5.5	3	0	22	107	4.9	4.7	4	0	18	102
5	5.0	5.4	3	0	22	107	4.9	5.0	3	0	21	115	4.0	4.6	3	0	22	106

MFQ:Mood and Feelings Questionnaire; **RCMAS**:Revised Childrens's Manifest Anxiety Scale**; LOI**:Leyton Obsessional Inventory

Table 12: Comparison of groups for primary and secondary outcome measures (continued)

Outcome	BPI						CBT						STPP					
measure	Mean	SD	Med	Min	Max	n	Mean	SD	Med	Min	Max	n	Mean	SD	Med	Min	Max	n
ABQ																		
Baseline	3.5	3.4	3	0	18	155	3.1	2.8	2	0	14	152	3.3	3.3	3	0	18	154
1	2.5	2.5	2	0	11	98	1.9	2.1	1	0	10	102	2.1	2.6	1	0	13	107
2	2.3	2.9	1.1	0	17	111	1.7	2.7	1	0	15.4	104	1.5	2.3	0	0	12	107
3	1.8	2.5	1	0	16	103	1.0	1.5	0	0	7	101	1.4	2.0	1	0	9	107
4	1.1	1.6	0	0	8	99	1.4	2.7	0	0	16	107	1.1	2.5	0	0	22	102
5	0.8	1.4	0	0	7	107	1.2	2.2	0	0	13	115	0.9	1.5	0	0	8.8	106
HoNOSCA																		
Baseline	18.9	6.0	19	0	37.9	148	18.4	6.0	18	0	35	143	18.2	6.3	18	0	35.8	144
1	14.5	6.5	14	1	30	88	14.1	6.4	14	1	29	91	14.6	6.9	13	0	32.5	96
2	14.3	7.5	14	0	36.1	101	11.9	6.8	11	0	32	96	12.9	6.2	13	0	34.7	94
3	12.0	8.7	11	0	39	88	9.7	7.2	8	0	31	81	10.3	7.6	8	0	33.8	88
4	9.5	6.9	8.3	0	27.4	88	8.5	7.3	6	0	31.4	86	8.6	5.8	8	0	23.8	83
5	8.2	6.2	7	0	28.4	98	7.3	5.2	6	0	20.1	92	8.2	7.2	7	0	30	85

ABQ:Antisocial Behaviour's Questionnaire; **HoNOSCA**:Health of the Nation Outcome Scale for Children and Participants

The hypotheses of the trial concern the treatment effect in the post treatment period (≥36 weeks).

The study had four hypotheses: Comparing CBT with STPP

[H1] CBT will show non inferiority effects to STPP at 52 weeks

[H2] STPP will show superiority effects compared to CBT at 86 weeks.

Comparing CBT and STPP with BPI

[H3] the specialist intensive interventions (CBT/STPP) will show superiority effects compared to BPI at 52 week

[H4] the specialist intensive interventions (CBT/STPP) will show superiority effects compared to BPI at 86 week

As described in chapter 8 (statistical methods), the mean differences were estimated at weeks 36, 52 and 86 post randomisation (i) between the two theory based treatments [STPP vs CBT = intensive therapies] and (ii) between the two theory based treatments and BPI [(CBT+STPP) vs BPI]. These mean differences were estimated using linear mixed effects (LME) models fitted to post treatment responses only (≥36 weeks from randomisation). As well as a main effect of treatment, a time by treatment interaction and other pre-specified covariates were included in this model details of which are given in the data analytic strategy (chapter 8, statistical methods).

Estimates of the time by treatment-interaction from these models and the main effects of models are given in appendix Table 17. To address the four hypotheses [H1-H 4] the time-point specific treatment effect averaged over baseline covariates, sometimes called the *marginal treatment effect*, was estimated from the model with a time with treatment interaction. The mean differences between treatments at the three time-points (36, 52 and 86 weeks post randomisation) are tabulated in Table 13.

We first considered the non hypothesis driven clinical outcome at 36 weeks consistent with the end of treatment phase. The difference between CBT and STPP was negative for the primary outcome (MFQ) and the secondary outcomes RCMAS, LOI and HoNOSCA (Table 13). For MFQ the differences showed a non significant reduction of -0.179 (p=0.929). For RCMAS, LOI and HoNOSCA the respected difference were also non significant -0.855 (p=0.621) , -0.816 (p=0.167) and -0.617(p=0.567). When the intensive treatment (CBT+STPP) was compared with BPI, the difference was -3.234 (95% c.i. -6.611 to 0.143,p=0.061) for MFQ at 36 weeks. For both RCMAS and LOI, the reduction was statistically significant at a 2.5% level suggesting benefit of the theory based treatment at this time-point on 2 of the secondary measures.

Moving to the hypothesis that CBT will shows non-inferiority compared to STPP at 52 weeks [H1] we need to consider the upper confidence limit of the difference in outcome between CBT and STPP. For non-inferiority to

be concluded we need the upper limit to be smaller than a clinically important difference. For the purpose of the sample size calculation this was assumed to be 5 points on the MFQ scale.

For all four measures in Table 13 the point estimate is negative and this represents a beneficial effect of CBT compared to STPP. For MFQ at 52 weeks the treatment effect estimate is -0.307 (95% c.i. -3.774 to 3.161). Since the upper limit (3.161) is less than a clinically important difference of 5 units, we can conclude that CBT is non-inferior to STPP at this time-point. The corresponding upper limits for RCMAS, LOI and HoNOSCA were 2.354, 0.452 and 1.078 respectively, that would appear also to support the hypothesis of non-inferiority.

Consider now the hypothesis that STPP will show superiority effects compared to CBT at 86 weeks [H2]. From Table 13 the treatment effect for CBT compared to STPP is -0.578 (95% c.i. -4.104 to 2.948). With the point estimate representing a slight benefit for CBT compared to STPP, there is no evidence to support this hypothesis (p=0.748). Similar, conclusions can be drawn for RCMAS (p=0.878) , LOI (p=0.906) and HoNOSCA (p=0.394).

Hypotheses [H3] and [H4] consider superiority of the *intensive treatment* against BPI at 52 and 86 weeks. At 52 weeks [H3] the difference is -2.806 (95% c.i. -5.790 to 0.177, p=0.065) for MFQ. Whilst this suggests a benefit at this time point for the *intensive treatment*, this difference is smaller than the 5 points difference hypothesized as clinically significant in the sample size calculation and is not statistically significant at a 2.5% level. Similar effects are observed for RCMAS (-2.81, 95% c.i.-5.43 to -0.21), LOI (-1.12, 95%c.i. -2.010 to -0.231) and HoNOSCA (-1.15 95% c.i.-2.601 to 0.293) with the effect being close to the 2.5% level for RCMAS (p=0.035) and statistically significant for LOI (p=0.014), but less so for HoNOSCA (p=0.118). At 86 weeks [H4] the beneficial effect of the intensive treatment compared to BPI is attenuated with the treatment effect for none of the four outcome measures being statistically significant at a 2.5% level.

The intra-cluster correlation coefficient (ICC) for therapist was estimated for the models by centring the time variable in the model. This gives the value of the ICC for therapist at the mid-point of follow-up. The estimate of the ICC was found to be negligible ($<10^{-7}$) for all models.

Outcome data gathered prior to 36 weeks after randomisation (assessments 1 & 2) were also summarized in Table 10. These data are not relevant to the hypotheses of this study. Inferential analyses of these data are included in the data analysis supplement (Table 18). When STPP was compared with CBT there were no significant treatment effects for the primary outcome MFQ (p=0.383) , RCMAS (p=0.681) or HoNOSCA (p=0.398) . Young people receiving STPP had a worse outcome on the LOI scale during this period

(Adjusted mean difference= 1.199, 95% c.i. 0.278 to 2.120, p=0.011). When the two intensive therapies were compared with BPI, there was no evidence of a treatment effect for MFQ (p=0.382), RCMAS (p=0.632) or HoNOSCA (p=0.646), and outcome for BPI lay between that for CBT(p=0.309) and STPP (p=0.120) for LOI (see Table 18).

Table 13: Difference in marginal mean scores for the primary and secondary outcome measures from the LME models with a treatment by time interaction – negative effects indicate treatment benefit

Outcome measure Primary	Time (weeks)	Treatment Effect	(95% c.i.)	p-value[a]
MFQ				
CBT - STPP	36	-0.179	(-4.088 to 3.731)	0.929
	52	-0.307	(-3.774 to 3.161)	0.862
	86	-0.578	(-4.104 to 2.948)	0.748
(CBT+STPP) - BPI	36	-3.234	(-6.611 to 0.143)	0.061
	52	-2.806	(-5.790 to 0.177)	0.065
	86	-1.898	(-4.922 to 1.126)	0.219
Secondary	Time	Treatment	(95% c.i.)	p-value
RCMAS				
CBT- STPP	36	-0.855	(-4.239 to 2.530)	0.621
	52	-0.663	(-3.680 to 2.354)	0.667
	86	-0.254	(-3.489 to 2.980)	0.878
(CBT+STPP) - BPI	36	-3.832	(-6.781 to -0.884)	0.011
	52	-2.818	(-5.432 to -0.205)	0.035
	86	-0.663	(-3.460 to 2.134)	0.642
LOI				
CBT - STPP	36	-0.816	(-1.972 to 0.341)	0.167
	52	-0.574	(-1.601 to 0.452)	0.273
	86	-0.062	(-1.091 to 0.967)	0.906
(CBT+STPP) - BPI	36	-1.249	(-2.258 to -0.240)	0.015
	52	-1.120	(-2.010 to -0.231)	0.014
	86	-0.847	(-1.736 to 0 .042)	0.062
HoNOSCA				
CBT - STPP	36	-0.617	(-2.733 to 1.499)	0.567
	52	-0.620	(-2.318 to 1.078)	0.474
	86	-0.626	(-2.066 to 0.814)	0.394
(CBT+STPP) - BPI	36	-1.410	(-3.221 to 0.401)	0.127
	52	-1.154	(-2.601 to 0.293)	0.118
	86	-0.611	(-1.819 to 0.598)	0.322

[a] to control for two comparisons 2.5 % significance level should be use to main a 5% significance level for any measure and time-point combination .

The trial had two binary outcome measures, (i) presence of a major depressive disorder (MDD) as determined by the K-SADS inventory , (ii) threshold of primary outcome (MFQ score > 25) indexing potential clinical caseness (45, 63). As mentioned above the Adolescent Behaviour Questionnaire (ABQ) was dichotomized for the purpose of analysis due to having a highly skewed distribution. The frequency distributions of these three measures by treatment and time-point are given in Table 14. With a reduced rate representing benefit for all three scales, there was a similar pattern to that observed in the continuous scales (see table 14) with CBT and STPP showing benefit at assessment 3 (week 36 assessment) . At assessment 5 (week 86) there is some suggestion of a difference between groups but the pattern was not consistent across measures.

A logistic GEE model was then fitted to all three outcomes for data gathered from week 36 onwards. This model was then used to estimate the difference in proportions at week 36, 52 and 86 averaged across covariates, that is the marginal difference in proportions between treatments. These differences are presented in Table 15.

At 36 weeks the adjusted difference of percentages between CBT and STPP was -6.4% (95% c.i. -20.6% to 7.8%, p=0.375). The corresponding differences for the MFQ and ABQ thresholds at this time-point were 2.5% (95% c.i. -0.098 to 0.148, p=0.688) and -6.8%(95% c.i. -0.186 to 0.051,p=0.263). Considering, the hypothesis of non-inferiority of CBT compared to STPP at 52 weeks [H1], for MDD the adjusted difference of proportions was -1.8% (-12.0% to 8.4%), for MFQ threshold it was 1.1% (-9.0% to 11.1%) and for ABQ threshold it was -4.0% (-13.5% to 5.5%). Whilst the adjusted differences are small the confidence intervals are quite wide and so the evidence to support non-inferiority is weak indicating these comparisons are under-powered. At 86 weeks [H2] there was no evidence for MDD (p=0.261), MFQ threshold (p=0.708) or ABQ of STPP (p=0.725) being superior to CBT.

There were no significant differences for the comparison of the intensive therapies against BPI at 36 weeks, 52 weeks [H3] or 86 weeks [H4] for presence of a major depressive disorder (MDD). The percentage of subjects with an MFQ score greater than 25 , the adjusted difference in proportions between intensive treatments and BPI as -12.2% (95% c.i. -23.1% to -1.35, p=0.028) at 36 weeks and -10.6% (95% c.i.1.5% to 19.7%, p=0.023) at 52 weeks [H3] . This reduced to a difference of 1.8%(-8.3% to 012.0%) at 86 weeks [H4]. Being derived from MFQ one would be expected these differences were broadly consistent with those for MFQ (see table 14).

For the threshold (ABQ>0) the intensive treatments were significantly improved at 36 weeks (Adj. diff -12.8% , 95% c.i. -23.8% to -1.9% ,p=0.022) , there was no difference significant difference for 52 weeks [H3] with p=0.102 or for 86 weeks [H4] with p=0.389.

In summary, across both continuous and binary outcome measure we conclude that outcome for CBT and STPP were broadly similar at 52 weeks [H1] and 86 weeks [H2]. Comparing the combined intensive treatments with BPI there was some suggestion that outcome was better at 52 weeks [H3], although this effect may not be clinically important. What treatment effect there were appeared to have largely dissipated by 86 weeks [H4].

Table 14: Number of subjects (%) for the binary outcome measure by follow-up assessment

	BPI			CBT			STPP		
Assess.	Freq.	Total	(%)	Freq.	Total	(%)	Freq.	Total	(%)
MDD (K-SADS positive or high clinical indication for Major Depressive Disorder)									
1	63	95	(66.3)	57	95	(60.0)	62	99	(62.6)
2	57	105	(54.3)	46	98	(46.9)	54	99	(54.5)
3	42	95	(44.2)	28	89	(31.5)	35	98	(35.7)
4	27	92	(29.3)	23	90	(25.6)	23	87	(26.4)
5	27	99	(27.3)	24	95	(25.3)	14	92	(15.2)
MFQ score >25									
Baseline	149	155	(96.1)	148	154	(96.1)	148	156	(94.9)
1	74	99	(74.7)	82	104	(78.8)	82	107	(76.6)
2	82	112	(73.2)	73	106	(68.9)	75	108	(69.4)
3	66	105	(62.9)	48	104	(46.2)	53	109	(48.6)
4	48	105	(45.7)	47	111	(42.3)	41	110	(37.3)
5	48	116	(41.4)	45	123	(36.6)	40	114	(35.1)
ABQ score ≥1									
Baseline	121	155	(78.1)	124	152	(81.6)	128	154	(83.1)
1	75	98	(76.5)	71	102	(69.6)	73	107	(68.2)
2	78	111	(70.3)	57	104	(54.8)	52	107	(48.6)
3	62	103	(60.2)	45	101	(44.6)	55	107	(51.4)
4	47	99	(47.5)	43	107	(40.2)	41	102	(40.2)
5	39	107	(36.4)	49	115	(42.6)	43	106	(40.6)

Table 15: Estimated treatment effect (adjusted difference in proportions) at 36, 52 and 86 weeks for the binary outcome measure from GEE models based on data from 36 weeks onwards post randomisation

Outcome Measure	Time (weeks)	Adjusted Difference in proportions	(95% c.i.)	p-value
MDD				
CBT - STPP	36	-0.064	(-0.206 to 0.078)	0.375
	52	-0.018	(-0.120 to 0.084)	0.727
	86	0.057	(-0.043 to 0.157)	0.261
(CBT+STPP)-BPI	36	-0.043	(-0.160 to 0.073)	0.465
	52	-0.053	(-0.142 to 0.035)	0.239
	86	-0.065	(-0.152 to 0.022)	0.145
MFQ >25				
CBT - STPP	36	0.025	(-0.098 to 0.148)	0.688
	52	0.011	(-0.090 to 0.111)	0.837
	86	-0.020	(-0.125 to 0.085)	0.708
(CBT+STPP)-BPI	36	-0.122	(-0.231 to -0.013)	0.028
	52	-0.106	(-0.197 to -0.015)	*0.023*
	86	-0.067	(-0.161 to 0.026)	0.158
ABQ score ≥ 1				
CBT - STPP	36	-0.068	(-0.186 to 0.051)	0.263
	52	-0.040	(-0.135 to 0.055)	0.408
	86	0.018	(-0.083 to 0.120)	0.725
(CBT+STPP)-BPI	36	-0.128	-0.238 to -0.019)	*0.022*
	52	-0.074	(-0.163 to 0.015)	0.102
	86	0.040	(-0.051 to 0.131)	0.389

[a] to control for two comparisons 2.5 % significance level should be use to main a 5% significance level for any measure and time-point combination .

Moderation of treatment effects

Moderator effects on the primary outcome were investigated by adding an interaction between the moderator variable and treatment allocation to the primary analysis model. Table 16 gives the estimates of the treatment by moderator effect for each of the moderator hypotheses proposed in the methods section (see chapter 7 for details of measures and chapter 8 for analytic strategy and hypotheses). A negative estimate in this table indicates that a higher score of the moderator lowered the MFQ for the treatment relative to the comparator, that is an increase in the beneficial treatment effect.

First, we hypothesized that young people with elevated dependency sub scale sum scores on the Depressive Experiences Questionnaire (DEQ) would have greater reduction in MFQ if they received STPP rather than BPI or CBT treatment than those with lower scores. Before 36 weeks the direction of the effect was consistent with our hypothesis but this was not statistically significant (p=0.168). After 36 weeks there was clearly no evidence of an effect (p=0.918).

Secondly, we hypothesized that young people with elevated self-critical sun scale sum scores on the Depressive Experiences Questionnaire would have a better response if they received CBT rather than either BPI or STPP treatment. The direction of the effect was consistent with our hypothesis both before and after 36 weeks. Before 36 weeks this was marginally statistically significant (0.053), with the effect being much smaller after thirty six weeks (p=0.384).

Finally, we hypothesized that higher total scale scores for rumination response style of thinking when depressed (RSS) would show a better treatment response for CBT than BPI or STPP treatment. There was little evidence of an effect either before (p=0.671) or after (p=0.976) thirty-six weeks. In this case, the direction of the effect was only consistent with our hypothesis when comparing CBT with BPI after 36 weeks.

In summary, there is some indication that CBT might be more beneficial for young people with elevated Depressive Experiences Questionnaire self-critical scores, but this effect applied to the treatment period rather than a long term benefit as evaluated in the follow up phase.

Table 16: Treatment moderator analyses for the primary outcome (MFQ) based on the LME model with main effects for treatment with a moderator by treatment interaction

	<36 weeks			≥ 36 weeks		
	Mod. Effect	(95% c.i.)	p-value	Mod. Effect	(95% c.i.)	p-value
DEQ Dependency STPP vs (BPI+CBT)	-0.21	(-0.51 to 0.09)	0.168	0.02	(-0.35 to 0.39)	0.918
STPP vs BPI	-0.29	(-0.64 to 0.06)		-0.01	(-0.44 to 0.43)	
STPP vs CBT	-0.13	(-0.48 to 0.23)		0.05	(-0.40 to 0.49)	
DEQ self-criticism CBT vs (BPI+ STPP)	-0.36	(-0.72 to 0.05)	0.053	-0.20	(-0.66 to 0.25)	0.383
CBT vs BPI	-0.42	(-0.85 to 0.02)		-0.21	(-0.74 to 0.32)	
CBT vs STPP	-0.31	(-0.72 to 0.10)		-0.20	(-0.73 to 0.33)	
Ruminative response scale CBT vs (BPI + STPP)	0.04	(-0.14 to 0.22)	0.671	0.004	(-0.23 to 0.23)	0.975
CBT vs BPI	0.02	(-0.18 to 0.22)		-0.06	(-0.31 to 0.19)	
CBT vs STPP	0.07	(-0.14 to 0.28)		0.08	(-0.18 to 0.35)	

Note, negative effects indicate benefit for high scores of moderators

Adverse events

We undertook a brief examination of potential side effects of psychological treatment defined using responses to a set of somatic items selected from existing self report scels in the study. This provides a brief proxy measure of the potential for psychological treatment to have negaitve effects and we focussed on a physical symptoms only. A description of the items and the findings are given in the statistical appendix.

Appendix Data Analysis Supplement

Table 17: Linear Mixed Effects (LME) models estimates of main effects of treatment and time with treatment interactions with therapist, participant and slope random effects for data from 36 weeks onwards post randomisation

Outcome measure	Treatment effect	(95% c.i.)	p-value[a]
Primary			
MFQ			
Time-treatment interaction			
STPP vs CBT	0.008	(-0.058 to 0.074)	0.812
CBT vs BPI	0.023	(-0.043 to 0.089)	
STPP vs BPI	0.031	(-0.035 to 0.097)	
(CBT+STPP) vs BPI	0.027	(-0.030 to 0.084)	0.361
Treatment main effect[c]			
STPP vs CBT	0.411	(-2.901 to 3.723)	0.808
CBT vs BPI	-2.591	(-5.860 to 0.678)	
STPP vs BPI	-2.179	(-5.487 to 1.128)	
(CBT+STPP) vs BPI	-2.385	(-5.226 to 0.456)	0.100
Secondary			
RCMAS			
Time-treat interaction			
STPP vs CBT	-0.012	(-0.732 to 0.049)	0.701
CBT vs BPI	0.069	(0.007 to 0.131)	
STPP vs BPI	0.057	(-0.005 to 0.120)	
(CBT+STPP) vs BPI	0.063	(0.009 to 0.117)	0.022
Treatment main effect[b]			
STPP vs CBT	0.488	(-2.450 to 3.425)	0.751
CBT vs BPI	-2.140	(-5.052 to 0.772)	
STPP vs BPI	-1.652	(-4.601 to 1.297)	
(CBT+STPP) vs BPI	-1.896	(-4.432 to 0.640)	0.116
LOI			
Time-treat interaction			
STPP vs CBT	-0.015	(-0.034 to 0.004)	0.120
CBT vs BPI	0.016	(-0.004 to 0.035)	
STPP vs BPI	0.0005	(-0.019 to 0.020)	
(CBT+STPP) vs BPI	0.008	(-0.009 to 0.025)	0.351
Treatment main effect[c]			
STPP vs CBT	0.318	(-0.659 to 1.295)	0.527
CBT vs BPI	-1.132	(-2.099 to -0.165)	
STPP vs BPI	-0.814	(-1.795 to 0.167)	
(CBT+STPP) vs BPI	-0.973	(-1.816 to -0.131)	0.024

[a] P-value based on a likelihood ratio test where a significance level is 0.025 should be used to control for two comparisons

[b] Treatment main effects are based on the time-treatment interaction model

[c] Treatment main effect is averaged across centred time since randomisation because there is no interaction between time and treatment

Table 17: Linear Mixed Effects (LME) model estimates of main effects of treatment and time treatment interactions with therapist, participant and slope random effects for data from 36 weeks onwards post randomisation (continued)

Outcome measure	Treatment effect	(95% c.i.)	p-value[a]
HoNOSCA			
Time-treat interaction			
STPP vs CBT	0.0002	(-0.039 to 0.039)	0.993
CBT vs BPI	0.016	(-0.022 to 0.054)	
STPP vs BPI	0.016	(-0.023 to 0.055)	
(CBT+STPP) vs BPI	0.016	(-0.017 to 0.049)	0.348
Treatment main effect[b]			
STPP vs CBT	0.612	(-0.785 to 2.008)	0.391
CBT vs BPI	-1.055	(-2.414 to 0.303)	
STPP vs BPI	-0.444	(-1.820 to 0.932)	
(CBT+STPP) vs BPI	-0.749	(-1.925 to 0.426)	0.207

[a] P-value based on a likelihood ratio test where a significance level is 0.025 should be used to control for two comparisons

[b] Treatment main effect is averaged across centred time since randomisation because there is no interaction between time and treatment.

Table 18: Linear Mixed Effects (LME) model estimates of main effect of treatment with therapist and participant random effects for data up to 36 weeks post randomisation

Outcome measure	Treatment effect	(95% c.i.)	p-value[a]
Primary			
MFQ			
Treatment main effect			
STPP vs CBT	1.215	(-1.511 to 3.941)	0.383
CBT vs BPI	-1.662	(-4.381 to 1.056)	
STPP vs BPI	-0.447	(-3.138 to 2.244)	
(CBT+STPP) vs BPI	-1.055	(-3.391 to 1.282)	0.382
Secondary			
RCMAS			
Treatment main effect			
STPP vs CBT	0.553	(-1.623 to 2.729)	0.618
CBT vs BPI	0.173	(-2.008 to 2.354)	
STPP vs BPI	0.726	(-1.421 to 2.873)	
(CBT+STPP) vs BPI	0.449	(-1.421 to 2.320)	0.632
LOI			
Treatment main effect[b]			
STPP vs CBT	1.199	(0.278 to 2.120)	0.011
CBT vs BPI	-0.478	(-1.401 to 0.444)	0.309
STPP vs BPI	0.721	(-0.187 to 1.628)	0.120
HoNOSCA			
Treatment main effect			
STPP vs CBT	0.623	(-0.821 to 2.068)	0.398
CBT vs BPI	-0.608	(-2.045 to 0.828)	
STPP vs BPI	0.015	(-1.402 to 1.432)	
(CBT+STPP) vs BPI	-0.297	(-1.528 to 0.934)	0.646

[a] P-value based on a likelihood ratio test where a significance level is 0.025 should be used to control for two comparisons.

[b] Due to a significant effect comparing STPP and CBT separate analyses are provided

Table 19: Population averaged odds ratios from logistic GEE models

Outcome measure	Odds Ratio	95%CI	p-value
MDD			
Time-treatment interaction			
STPP vs CBT	0.99	(0.97 to 1.00)	0.139
(CBT+STPP) vs BPI	1.00	(0.98 to 1.01)	0.572
MFQ>25			
Time-treatment interaction			
STPP vs CBT	1.00	(0.99 to 1.02)	0.509
(CBT+STPP) vs BPI	1.01	(0.99 to 1.02)	0.360
ABQ score >0			
Time-treatment interaction			
STPP vs CBT	0.99	(0.98 to 1.01)	0.225
(CBT+STPP) vs BPI	1.02	(1.00 to 1.03)	0.009

A9.3 Adverse events

The following five items from the RCMAS sub-scale : breathing problems, sleep disturbances, drowsy/tiredness, nausea, and sweating and one from the MFQ sub-scale: restless/overactive were used to generate a physical adversity score ranging from 0-6 where for each item a zero score was assigned if the response was "never" otherwise this was assigned a value of one . Pro-rating was used if 1 or 2 items of the 6 items were missing using all the available data for the MFQ or RCMAS sub-scales, respectively. The summary statistics are shown in Table 20.

Table 20: Summary statistics for adverse event score based on 6 adverse event items

	BPI					CBT					STPP				
Visit	Mean	SD	Med	Min	Max	Mean	SD	Med	Min	Max	Mean	SD	Med	Min	Max
0	5.0	1.1	5	1	6	5.1	1.0	5	2	6	5.0	1.1	5	2	6
1	4.4	1.5	5	0	6	4.6	1.3	5	2	6	4.4	1.5	5	0	6
2	4.2	1.6	4	0	6	4.0	1.5	4	0	6	4.2	1.6	4	0	6
3	4.1	1.6	4	0	6	3.6	1.6	4	0	6	3.6	1.7	4	0	6
4	3.5	1.8	3.5	0	6	3.5	1.9	4	0	6	3.2	1.9	3	0	6
5	3.3	1.8	3.5	0	6	3.4	1.9	4	0	6	3.2	1.8	3	0	6

Inspection of the data shows no observable differences between treatment groups over the course of the study. The decline in adverse event reporting over the 5 assessments is relatively consistent with a persistent lessening of positive responses from baseline recruitment through to end of follow up.

The results whilst showing no treatment differences in somatic side effect profile as defined is unlikely to provide a comprehensive estimate of psychological and social side or adverse effects that may accrue from psychological treatment of depressed adolescents. Currently however there are no formally adopted methodologies for the measurement of such experiences although the filed is beginning to recognise the need for such (111) (112).

Chapter 10

Economic evaluation results

Data completeness

At 86 weeks, full CA-SUS service use data was available for 94 participants (61%) in the CBT group, 91 (58%) in the STPP group and 92 (59%) in the BPI group, which was 60% of the total number randomised. Baseline demographic and clinical characteristics of cases with complete and missing service use data were compared using standard t-tests and anova, as appropriate, including age, sex, ethnicity, region and MFQ. No significant differences were identified.

Outliers

The cost data were examined to consider the impact of highly influential observations, defined by Weichleet et al (113) as those whose exclusion result in major changes in the results. Two observations were identified as above the 99th percentile for total costs, but only one of these would have increased parameter estimates by a factor of 1.4. Therefore this one observation was removed from the main analysis as recommended (113).

Resource use

All resources used over the 86-week follow-up period are summarised by group in Table 21.

Trial treatment

For the sample of participants with full service use information, the average number of treatment sessions attended by the young people was 7.97 in the BPI group, 9.73 in the CBT group and 13.85 in the STPP group. The numbers differ slightly from those reported in chapter 9 because they are the results for the sub-sample of participants for whom we had full service use data. On average, the number of sessions attended was lower than the number of sessions planned (BPI 12 sessions, CBT 20 sessions, STPP 28 sessions).

Other health and social services

Overall there was little difference between randomised groups in levels of service use over the 86 week follow-up (see Table 21). Levels of mental health admissions were low (less than 2%) across all randomised groups. There were slight variations in non-mental health admissions, with 13% of the STPP group being admitted compared to 8% in the BPI group and 5% in the CBT group. Overall up to a fifth of participants had a non-mental health admission. Accident and emergency attendances were not uncommon (BPI 23.40%, CBT 12.63%, STPP 19.57%), but average levels of attendance were less than one contact in each group.

GPs were the most widely used service, accessed by 66%, 72% and 64% of participants in the BPI, CBT and STPP groups, respectively. Use of community mental health services, excluding the trial interventions, was highest in the BPI group (46% of BPI participants) compared to 38% and 29% of the CBT and STPP groups, respectively. Rates of social services contacts were also highest in the BPI group.

Antidepressant medication

Over the course of the study, patients were allowed to receive an SSRI in addition to psychological treatment if they met National Institute of Clinical Excellence guidelines for combined treatment to aid clinical remission by end of treatment. The proportion of participants prescribed antidepressant medication at any point over the 86-week follow-up was around 30% in each group.

Table 21: Service use (unit), Mean, SD, over 86-week follow-up

	BPI (n=96)			CBT (n=95)			STPP (n=92)		
	Mean	SD	%*	Mean	SD	%*	Mean	SD	%*
Treatment (sessions)	7.97	5.19		9.73	6.54		13.85	10.41	
Mental health inpatient (night)	0.02	0.20	1.04	0.08	0.72	2.11	0.00	0.00	0
Non-Mental health inpatient (night)	0.26	1.06	8.34	0.11	0.57	5.26	0.42	1.54	13.04
Mental health outpatient (attendance)	0.01	0.10	1.04	0.05	0.51	1.05	0.00	0.00	0
Non-mental health outpatient (attendance)	0.65	1.83	18.75	0.35	1.19	13.68	0.75	1.90	23.91
Accident and emergency (attendance)	0.45	1.61	22.91	0.14	0.38	12.63	0.35	0.80	19.57
General practitioner (contact)	2.79	5.00	66.67	2.40	4.07	71.58	2.60	3.79	64.13
Community medical services (contact)	0.12	0.43	8.33	0.09	0.49	5.26	0.37	2.26	4.35
Community mental health services (contact)	4.93	11.12	45.83	5.64	14.08	37.89	3.80	10.85	29.35
Community social services (contact)	1.33	3.74	20.83	0.95	4.02	11.58	6.88	62.32	14.13
Education support services (contact)	1.32	5.18	25.00	1.61	6.90	15.79	3.11	11.00	27.17
Antidepressant medication			30.77			28.57			31.73
Other medication			2.13			4.21			4.34

*% of participants in group using this service at least once

Total cost

Treatment costs

On average the cost of the trial interventions was lowest for CBT (£904.57) and highest for STPP (£1396.72), with BPI costing £1292.91. These differences reflect variation in the number and duration of treatment sessions (reported in Table 21) and the cost of the professionals providing the therapy, summarised in Table 2.

Total costs over follow-up

The broadly similar levels of service use reported in Table 21 translated into similar total health, social care and education costs per participant over the 86 week follow-up across the three groups: £1368.04 in BPI, £1459.26 in CBT and £1668.51 in STPP. Including the cost of the trial interventions generated total costs per participant over the 86 week follow-up of £2678.39 for the BPI, £2379.01 for CBT and £3081.70 for the STPP, see Table 22.

The results of the between group comparisons, detailed in Table 23, show that there were no significant differences in costs between groups. Bootstrapped confidence intervals were similar to those calculated from the linear regression models so are not presented here.

Table 22: Total cost per participant (£), Mean, SD, over 86-week follow-up

	BPI (n=92)		CBT (n=92)		STPP (n=91)	
	Mean	SD	Mean	SD	Mean	SD
Health, social care and education costs	1368.04	1368.04	1459.26	3481.02	1668.51	3425.68
Treatment costs	1292.91	1292.91	904.57	607.25	1396.72	1133.41
Total costs	2678.39	2678.39	2379.01	3643.85	3081.70	3573.17

Table 23: Between group differences in total costs over 86-week follow-up

	Coefficient	95% confidence interval	p-value
CBT versus BPI (n=180)	-338.54	(-1333.17 to 656.09)	0.503
STPP versus BPI (n=174)	609.55	(-406.73 to 1625.83)	0.238
CBT versus STPP (n=178)	-709.23	(-1836.04 to 417.58)	0.216

* Adjusted for region and baseline cost, behavioural disorder and antidepressant use

Outcomes

Health-related quality of life

EQ-5D scores at baseline and all follow-up points are detailed in Table 24. Utility scores were generally higher in the CBT group compared to BPI and STPP, where a higher score denotes higher levels of health-related quality of life. However, differences were small and at the 86 week follow-up, scores were marginally higher in the BPI group followed by the STPP group. The QALYs show very little between group differences: CBT group 1.228 QALYs, STPP 1.246 QALYs and BPI group 1.241 QALYs. There were no significant between group differences in QALYs as shown in Table 25.

Table 24: EQ-5D score and QALYs over 86-week follow-up*

Assessment point		BPI		CBT		STPP	
	n	Mean	SD	Mean	SD	Mean	SD
Baseline	447	0.596	0.275	0.578	0.281	0.569	0.258
t1 (week 6)	303	0.622	0.278	0.685	0.236	0.674	0.275
t2 (week 12)	310	0.713	0.236	0.714	0.267	0.680	0.259
t3 (week 36)	290	0.730	0.262	0.797	0.227	0.765	0.233
t4 (week 52)	295	0.771	0.227	0.803	0.232	0.792	0.257
t5 (week 86)	307	0.817	0.228	0.780	0.256	0.808	0.240
QALY	294	1.241	0.270	1.228	0.304	1.246	0.293

*Higher EQ-5D scores and higher QALYs denote better quality of life

Table 25: Between group differences in QALYs over 86-week follow-up

	Coefficient	95% confidence interval	p-value
CBT versus BPI (n=195)	-0.009	(-0.091 to 0.074)	0.839
STPP versus BPI (n=193)	0.000	(-0.081 to 0.082)	0.992
CBT versus STPP (n=200)	-0.019	(-0.103 to 0.064)	0.648

*Adjusted for region and baseline cost, behavioural disorder and antidepressant use

Cost-effectiveness analysis

CBT v BPI

For the CBT versus BPI comparison, CBT is less costly but slightly less effective in terms of QALYs than BPI. As a result, the replications produced in the scatterplot in Figure 8 are mainly in the South-West and South-East quadrants reflecting lower costs in the CBT group (points below the x-axis) and the very small difference in outcomes between the two groups (points evenly spread across the y-axis). The cost-effectiveness acceptability curve (CEAC) in Figure 9 shows that for all levels of willingness to pay per QALY there is a higher probability that CBT is more cost-effective than BPI.

Figure 8: Scatter plot of differences in costs versus differences in QALYs for CBT versus BPI

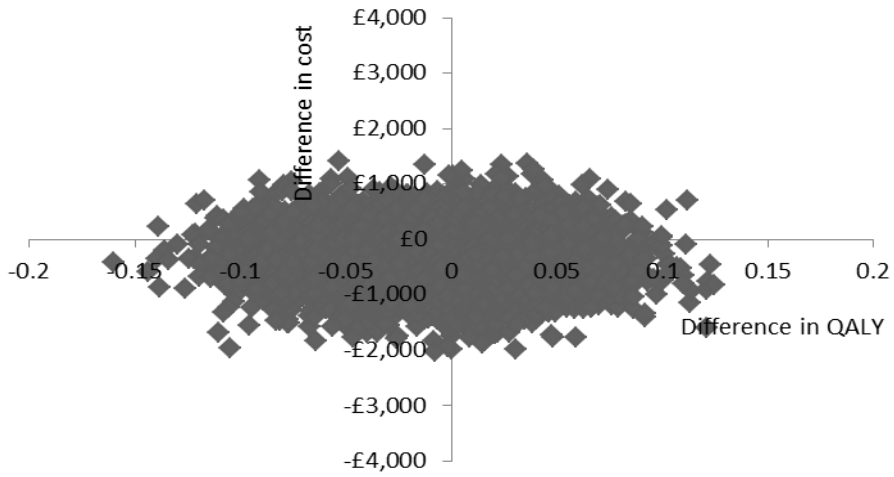
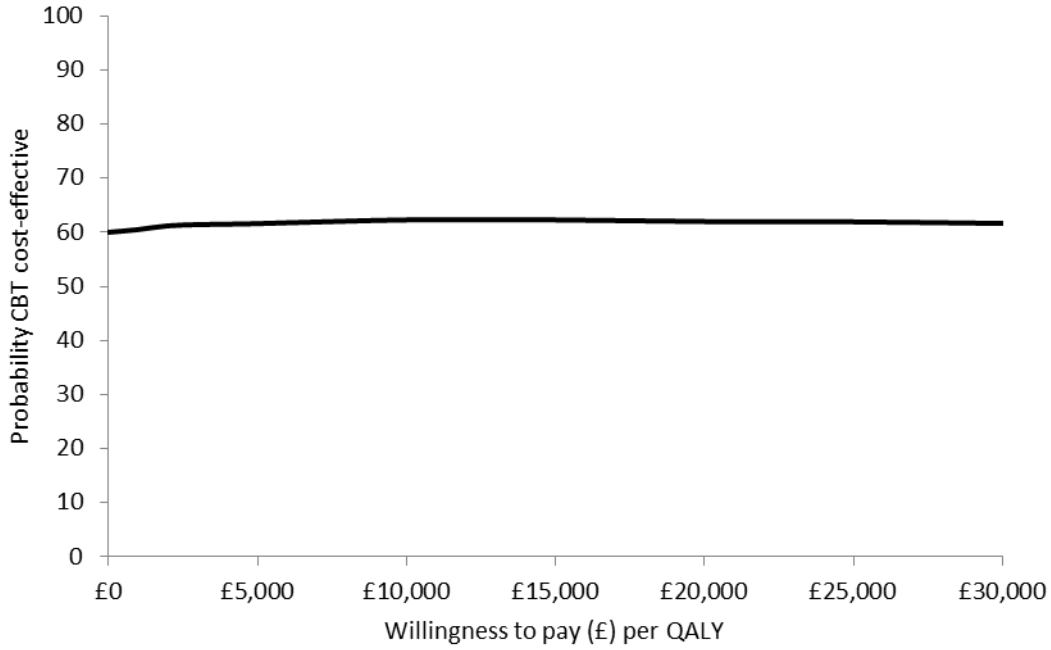


Figure 9: Cost-effectiveness acceptability curve showing the probability that CBT is cost-effective compared to BPI for different values a decision maker might be willing to pay for improvements in QALYs



STPP v BPI

For the STPP versus BPI comparison, costs were on average £403 more in the STPP group than the BPI group and QALYs were equal. The bootstrapped replications for STPP v BPI are shown in Figure 10. The majority are in the North-East and North-West quadrants, reflecting the higher costs in the STPP group (points above the x-axis). The CEAC in Figure 11 shows that there are no willingness to pay values where the probability of STPP being cost-effective compared to BPI is greater than 23%, within the £20,000-£30,000 ceiling level of willingness to pay considered acceptable by NICE (101).

Figure 10: Scatter plot of differences in costs versus differences in QALYs for STPP versus BPI

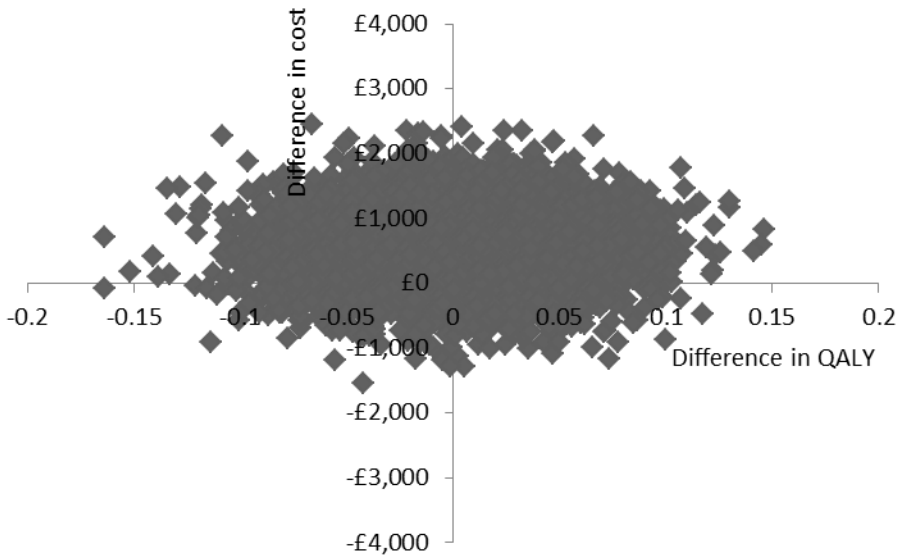
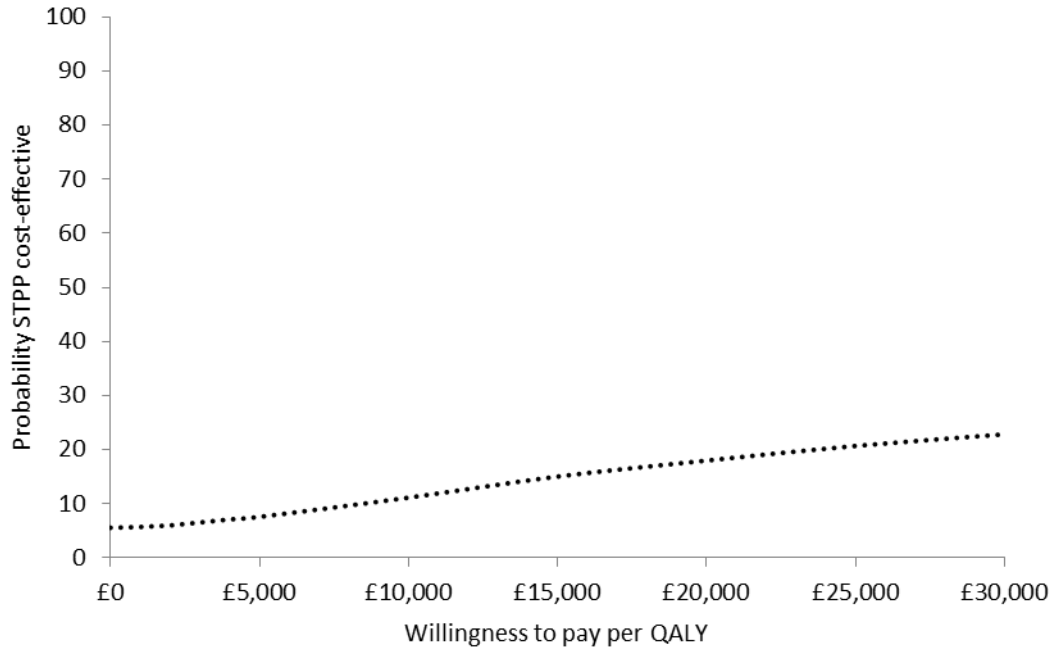


Figure 11: Cost-effectiveness acceptability curve showing the probability that STPP is cost-effective compared to BPI for different values a decision maker might be willing to pay for improvements in QALYs



CBT v STPP

Comparing the two intensive psychological treatments, CBT and STPP, total costs per participant over the 86 week follow-up were on average £703 lower in the CBT group and outcomes 0.02 QALYs worse. As a result, the replications in the scatterplot in Figure 12 are mostly in the South-West quadrant. The CEAC shown in Figure 13 suggests that the probability that CBT is cost-effective compared to STPP for all willingness to pay values is greater than 50%.

Figure 12: Scatter plot of differences in costs versus differences in QALYs for CBT versus STPP

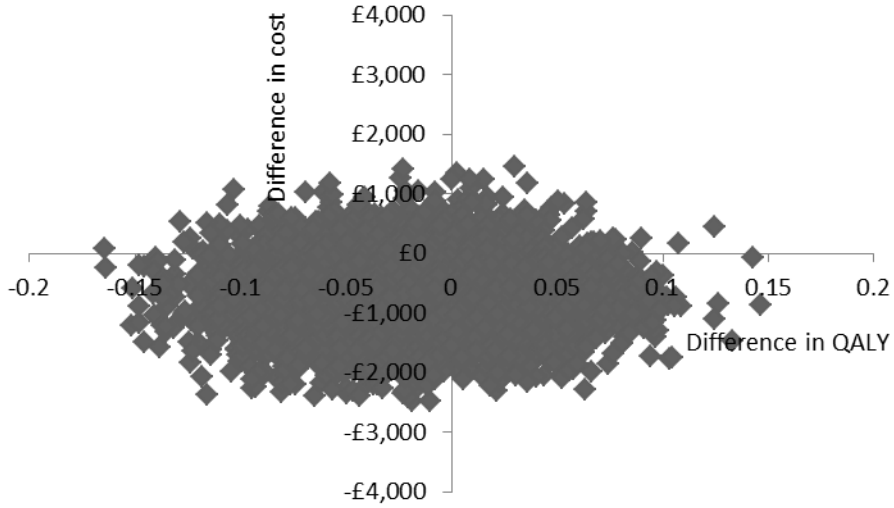
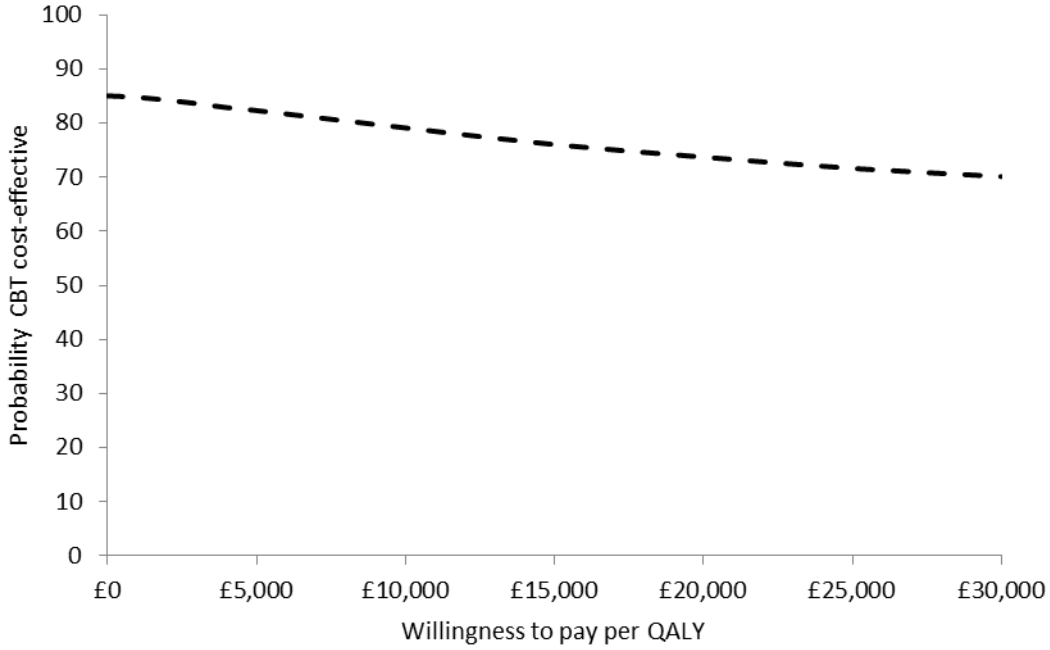


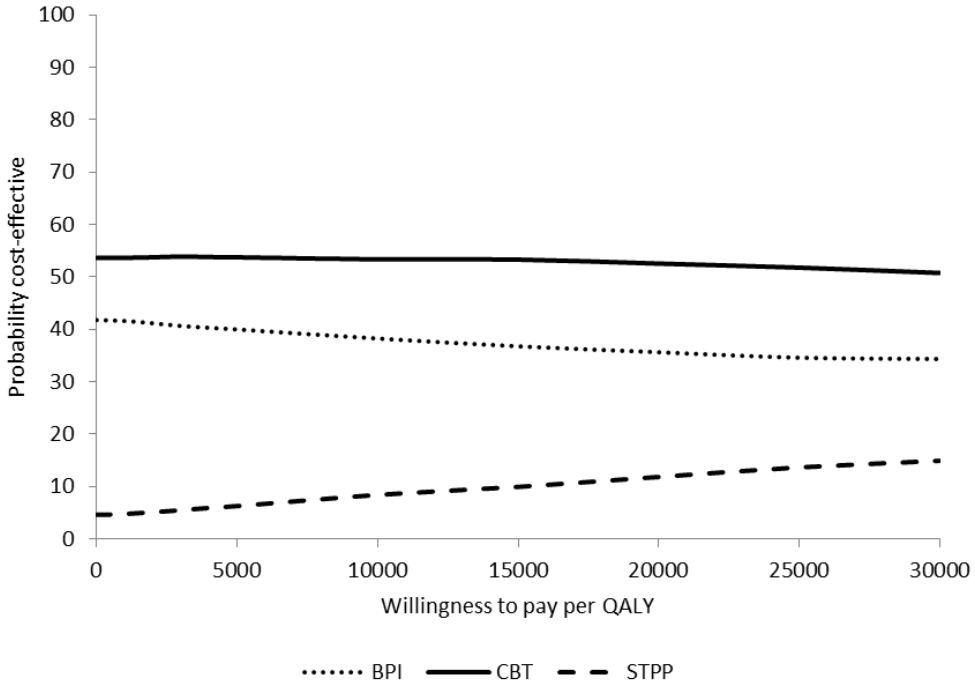
Figure 13: Cost-effectiveness acceptability curve showing the probability that CBT is cost-effective compared to STPP for different values a decision maker might be willing to pay for improvements in QALYs



CBT v STPP v BPI

The three interventions were compared head to head in a three-way comparison. The CEACs in Figure 14 show that for all values that a decision maker might be willing to pay for a QALY, CBT has the largest probability of being cost-effective.

Figure 14: Cost-effectiveness acceptability curve showing the probability that BPI, CBT and STPP are cost-effective for different values a decision-maker might be willing to pay for improvements in QALYs



Sensitivity analysis

The results of the sensitivity analyses are detailed in Tables 26 and 27. Multiple imputation did not alter the direction of the differences in cost, nor did re-analysis using cost per week rather than cost over the entire follow-up period. Including an estimate of the cost of sessions that were scheduled but which the young person did not attend, however, altered the order between the three interventions.

For the sample with full economic data, the average number of sessions that were offered but were not attended were 3 in the BPI group, 14 in the CBT group and 6 in

the STPP group. The inclusion of the cost of these sessions (at 50% of the cost of a full session) resulted in the average cost of CBT (£3,050) becoming more expensive than the BPI mean cost (£2,939), with STPP remaining the most costly group (mean cost £3,364).

Whilst there remain no statistically significant differences in cost between the groups, this change in direction impacts upon the cost-effectiveness analyses for the comparison of CBT and BPI, with CBT being dominated by BPI (costs higher and outcomes very slightly lower). Figure 15 shows the scatter plot for this comparison; the majority of the replications are in the North-East and North-West quadrants denoting higher costs in the CBT group (points above the x-axis). The very similar outcomes mean that the CEAC in Figure 16 suggests that the probability that CBT is cost-effective compared to BPI is less than 50% for all values a decision maker might be willing to pay for a QALY. Figure 17 shows a head to head comparison of all three groups in terms of cost-effectiveness and including a cost for sessions missed. It demonstrates that there is a higher probability of BPI being cost-effective compared to CBT and STPP, for all values of willingness to pay.

Table 26: Sensitivity analyses for costs (£) over 86-week follow-up

	BPI		CBT		STPP	
	Mean	SD	Mean	SD	Mean	SD
Base case analysis	2678.39	2881.89	2379.01	3643.85	3081.70	3573.17
Non-attendance at 50% cost	2907.30	2939.08	3050.05	5891.69	3364.14	3563.08
Multiple imputation	-	-	-	-	-	-
Total cost per week	28.76	31.63	25.25	38.35	32.42	35.84

Table 28: Between group differences for sensitivity analysis at 86-week follow-up

Comparison	Sensitivity analysis	Coefficient	95% confidence interval	p-value
CBT v BPI	Base case	-338.54	(-1333.17 to 656.09)	0.503
	Non-attendance at 50% cost	185.15	(-392.71 to 1657.16)	0.225
	Multiple imputation	-425.07	(-1384.58 to 534.43)	0.381
	Total cost per week	-3.95	(-14.58 to 6.68)	0.464
STPP v BPI	Base case	609.55	(-406.73 to 1625.83)	0.238
	Non-attendance at 50% cost	632.21	(-392.71 to 1657.16)	0.225
	Multiple imputation	448.95	(-609.77 to 1507.66)	0.399
	Total cost per week	6.12	(-4.47 to 16.72)	0.256
CBT v STPP	Base case	-709.23	(-1836.04 to 417.58)	0.216
	Non-attendance at 50% cost	-429.79	(-1955.24 to 1095.65)	0.579
	Multiple imputation	-891.47	(-1951.81 to 168.86)	0.098
	Total cost per week	-7.46	(-19.10 to 4.17)	0.207

* All adjusted for region and baseline eq-5d score, behavioural disorder and antidepressant use

Figure 15: Sensitivity analysis – Scatter plot of differences in costs versus differences in QALYs for CBT versus BPI with non-attendance at 50% session cost

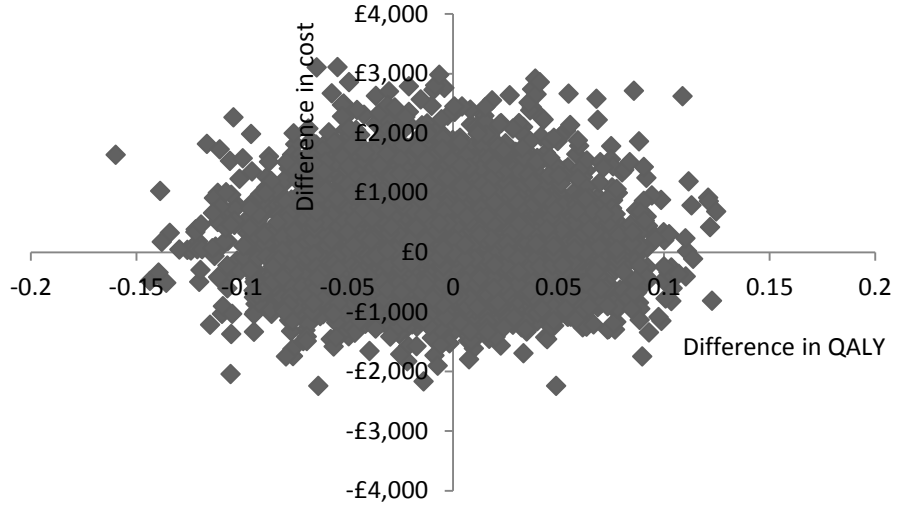


Figure 16: Sensitivity analysis – Cost-effectiveness acceptability curve showing the probability that CBT is cost-effective compared to BPI for different values a decision maker might be willing to pay for improvements in QALYs with non-attendance at 50% session cost

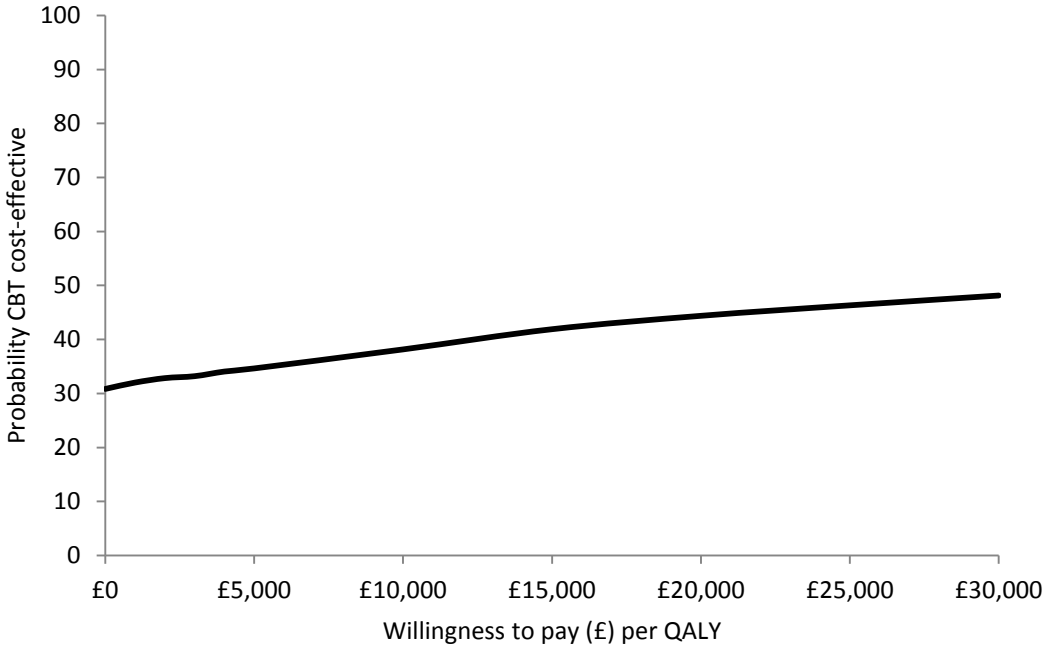
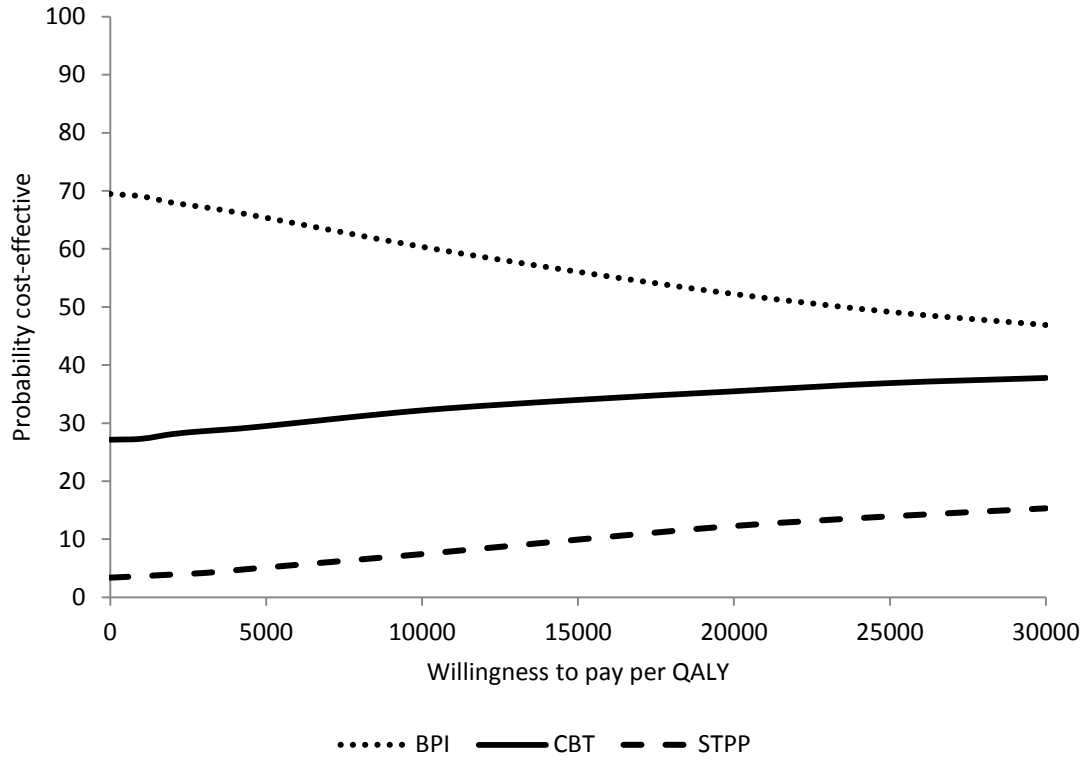


Figure 17: Sensitivity analysis – Cost-effectiveness acceptability curve showing the probability that CBT, STPP and BPI are cost-effective for different values a decision-maker might be willing to pay for improvements in QALYs with non-attendance at 50% session cost



Chapter 11

Discussion

This randomised controlled trial of the treatment of adolescents referred to routine CAMHS with DSM IV Major Depressive Disorder found no evidence for the superiority of two specialist intensive therapies Cognitive Behaviour Therapy (CBT) or Short Term Psychoanalytic Therapy (STPP), compared to a shorter practise based brief psychosocial intervention (BPI) for maintaining the reduction of self reported depression symptoms observed at 36 weeks and reassessed over 2 follow up assessments of 52 and 86 weeks after randomisation. All three treatment conditions were manualised. There were no clear cut indications that either specialist treatment was cheaper or more cost-effective than BPI. Average self reported depression scores improved substantially, from baseline to follow up points across all three treatment groups. Whether or not this change can be casaully attributed to the treatments cannot be determined because, for ethical reasons, there was no 'no treatment' control group.

While this study provided a clear negative finding for its main hypothesis, there were results that whilst not definitive, are worth highlighting as further research may elucidate their potential importance for policy decisions and clinical practice. These refer to 1) timing of the primary outcomes and outcomes other than depressive symptoms, 2) the economic analyses, 3) the new treatment, Brief Psychosocial Intervention 4) the observed non response to treatment 5) the potential implications for clinical practice.

Timing of outcomes

The results showed a similar trend, seen across several symptom measures of depression, anxiety and obsessionality, for outcome scores in the combined specialist intensive treatments (CBT +STPP) group to be somewhat lower than that for BPI at 52 weeks after randomization, which was also seen at 36 weeks corresponding approximately to end of treatment. This is partly illustrated in figure 7, showing the differences in individual scale scores for each treatment group. Although individual

differences are not significantly different there is a suggestion that the combined analysis (CBT+STPP) reveal differences were close to statistical significance at the 2.5% level in Table 13. None of these mean differences were large however and the clinical significance of somewhat lower sum scores is uncertain. For example the depression symptoms were significantly lower for the specialist treatment group with a mean difference of -3.28 at 36, -2.8 at 52 weeks and -1.98 at 86 weeks follow up assessment. Further although the mean difference is less than 5 points on the MFQ implying this unlikely to be clinically meaningful the confidence limits hint at a some patients showed greater individual differences in response that may decline by 86 weeks.

Whilst multiple analyses across measures will tend to inflate Type I errors, we note the consistency of the pattern of these results rather than the statistical or clinical significance of any one analysis. The average effect size across the four quantitative outcomes (Table 13) were similar ranged from 0.17 to 0.21 at 52 weeks. A slightly larger effect was observed at 36 weeks ranging from 0.18 to 0.29. Equally there was a consistent trend across these symptom measures for this difference to be much smaller, and entirely non-significant by 86 weeks with effect sizes ranging from 0.04 to 0.17. The findings provide a pointer to the need for further research into timescales for symptomatic recovery from depression. The fall in symptoms deserves further investigation to establish either a meaningful difference for some receiving specialist treatments in relation to BPI or that the finding is not important. Further investigation may also reveal whether there are individual differences of value in response to treatment and whether or not psychosocial adjustment correlates or decouples from symptom change over time.

Economic analyses

On average, the observed cost of the trial treatments for those where full data was available in the main analysis was lowest for CBT and highest for STPP. Whilst BPI was intended to be brief compared to both alternative treatments, in practice the average number of BPI treatment sessions attended ~~were~~ was not substantially lower than in the CBT group (likely due to ~~-~~non~~-~~-attendance of the planned longer term therapies)~~-~~ and, coupled with higher average therapist costs, BPI was estimated to cost somewhat more than CBT although these differences were not statistically significant.

The inclusion of a cost for non-attendance, however, reversed this finding, making CBT more expensive than BPI as a result of a larger difference between sessions offered and sessions attended. With a higher number of sessions attended per person, STPP remained the most expensive of the three treatments. Use of all other health and social services over the follow-up period were broadly similar, thus differences in total costs were primarily influenced by the cost of the trial treatments. In terms of cost-effectiveness, differences between groups were marginal and sensitive to the inclusion of the cost of sessions offered but not attended.

Brief Psychosocial Intervention

The protocol for high quality active clinical care, referred to in this report as Brief Psychosocial Intervention (BPI), was developed for this study in order to ensure that the comparison condition was coherent and informed by all available research, and that it did not include active technical components of CBT or STPP. Since BPI was designed as a high quality 'active' control condition, it was not evaluated against an intervention predicted to be less effective. This means that we cannot determine whether it was itself either efficacious (as there is no passive control condition) or clinically effective in the absence of an appropriate clinical control group such as waiting list. However as outcomes at 86 weeks were non-inferior in the BPI group, it merits further consideration as a potential treatment. BPI was a multifaceted intervention with several elements (see chapter 4 for details) that may have contributed to improvement in self reported depression, including psychoeducation, support for increased activities, and attention to the young person's family and school environment. It remains to be determined whether some or all of these elements may contribute to treatment effectiveness, and also whether other aspects of BPI were important. For example BPI may have been more tailored to variations in young persons' wishes or problems, consistent with evidence for advantages of personalised approaches to adolescent depression (114).

Treatment resistance and the maintenance of clinical high risk status

A substantial proportion of patients (approximately 25%) continue to meet diagnostic criteria for unipolar major depression by 86 weeks. A further 15% report depressive

symptoms higher than the cut off score (>26) for potential caseness. Only 285 (60%) of the sample were however available for full clinical assessment at this time point. This findings suggests that as there were no treatment group differences there is a degree of treatment resistance or non-compliance in this cohort overall. Current therapeutic interventions used in this study appear to be potentially ineffective in a proportion of cases, an observation that resonates with prior trial findings on depressed adolescents (10, 11). This is a serious negative outcome that requires further investigation as providing potentially ineffective treatments to depressed adolescents is not good clinical practise. There is a marked lack of understanding regarding treatment failures and resistant depressions in this age range. There is a suggestion that more clinically severe presentations, the presence of suicidality and obsessive compulsive disorder at presentation are associated with less treatment response by 28 weeks post randomisation (115). Furthermore the presence of non-suicidal self injury at randomisation may be predictors of increased suicidality and therefore a risk for treatment non response (116). These observations require replication and further investigation than they have received hitherto as identifying patients unlikely to respond to available therapies is an important clinical priority.

Reducing symptom recurrence risk following treatment

Preventing clinical diagnostic relapse by maintaining low depressive symptoms is potentially of substantial clinical and cost value as even successfully treated adult patients may suffer on average between 5 to 9 episodes over the life course at considerable personal and economic cost to the individual and society (1, 117, 118).

The likelihood of relapse following successful treatment in depressed adolescents is likewise substantial occurring in 50%-75% of successfully treated patients (28-30).

These studies emphasizes the potential value in lowering prospective diagnostic risk by reducing depressive symptoms in the medium term. Elevated symptom levels above the population norm predict the emergence of major depression in adolescents, correlate with persisting depressive disorders and predict relapse in adults with a history of depression (90, 119-122).

The current findings are therefore encouraging as the lowered depressive symptoms by 86 weeks associated with these psychological treatments is in the direction of prevention of diagnostic relapse.

Strengths and limitations

This study had many strengths including that participants were representative of depressed adolescents referred to a comprehensive health provision, across diverse regions of the UK, that they all met research diagnostic criteria for DSM IV Major Depressive Disorder, they were randomized remotely from the research team, and follow up assessments were completed blind to treatment group assignment on over 75% of those randomized. The sample size was greater than any previous studies and this is the first time a trial of depressed adolescents has used follow up 86 weeks post randomisation as a end point of the trial. Each of the three treatments was manualised, and adherence assessments demonstrated expected differences between them. However the accuracy of the ratings of adherence may have been limited by low inter-rater reliability for the adherence measures. Clinicians who delivered each type of treatment were characteristic of those who deliver these treatments in routine clinical practice, which adds confidence to the findings.

The inclusion of a manualised comparison condition, BPI, made it more likely that the quality of the treatment was similar across arms, enabled adherence to be assessed, and clarified the focus for supervision. It also ensured that the comparison condition did not include key features of STPP and CBT. The issue of overlap between therapies was evaluated with a satisfactory finding from tape analyses that the therapists were delivering treatment as per protocol and that these were significantly different between the three groups. Nevertheless it is acknowledged that some overlap in therapy processes may occur. In the absence of specific knowledge about the mechanisms of particular psychological treatment it may be that there are commonalities that are shared and exert sufficient clinical effects to diminish differences between specific treatment protocols in this study. Further research on the mechanisms that lead to change when we expose depressed adolescents to psychological treatment is suggested form these results to disaggregate general from specific therapy effects.

The economic results were limited by missing data, which was higher than for the primary clinical outcome measure (60%). However, multiple imputation of missing did not change the results of the analysis, giving some confidence in the conclusions. The economic results, shown to be sensitive to the inclusion of the cost of participant non-attendance, are also limited by the reliance of this sensitivity analysis on accurate reporting by therapists. Data were calculated as number of sessions offered minus number of sessions attended. However, more detailed information, for example on whether sessions offered were cancelled or rearranged, was unavailable. This data is therefore a proxy for DNA rates and so should be interpreted cautiously. The assessment of cost-effectiveness on the basis of the EQ-5D raises questions about the validity of the measure in an adolescent sample with depression. Although there is some evidence to support the use of the measure in this population (59), the evidence is relatively weak and further research into measures appropriate for young people with mental health problems is needed.

Conclusions

Overall this randomised controlled trial demonstrates no superiority for specialised more intensively delivered therapies of CBT and STPP than a high quality active comparator of Brief Psychosocial Intervention in maintaining the reduction of depressive symptoms after treatment through to 86 weeks post randomisation.
All three treatments were associated with similar cost effectiveness and improved quality of life over the follow up period.

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Contributions

Ian Goodyer (Professor of Child and Adolescent Psychiatry, University of Cambridge) designed the study, obtained the research funding, wrote papers and wrote papers arising from the study.
Shirley Reynolds (Professor of Evidence Based Psychological Therapies University of Reading) designed the CBT protocol, contributed to the study design including the fidelity and adherence study and wrote papers arising from the study.
Barbara Barret (Senior lecturer in Health Economics, Kings College London), undertook the health economics analysis and wrote the health economics chapter.
Sarah Byford (Professor of Health Economics, Kings College London) designed and undertook the health economics analysis, contributed to the grant application, wrote the health economics chapter.
Bernadka Dubicka (Consultant Psychiatrist and Lecturer, University of Manchester) contributed to measurement and study design and the BPI clinical protocol.
Jonathan Hill (Professor of Child and Adolescent Psychiatry. School of Psychology & Clinical Language Sciences, University of Reading) contributed to measurement, selection and study design whilst Professor of Child and Adolescent Psychiatry at the University of Manchester.
Fiona Holland, (Research Associate in statistics, University of Manchester) undertook data analysis.
Raphael Kelvin, (Consultant Child and Adolescent Psychiatrist, Cambridge and Peterborough NHS Foundation Trust, Associate Lecturer, University of Cambridge) wrote the clinical manual and protocol for BPI, designed the fidelity and adherence study, wrote papers arising from the study.
Nick Midgley (Academic Director, Child and Adolescent Psychotherapy Child and Adolescent Psychotherapist, Anna Freud Centre) contributed to measurement and methods, wrote the STTP protocol and manual, designed fidelity and adherence study, wrote papers arising form the study.
Chris Roberts (Professor of Biostatistics, University of Manchester) contribute to grant application, designed the data analysis wrote papers arising form the study.

Rob Senior (Senior Research fellow UCL, Medical Director and honorary Consultant Tavistock and Portman NHS Foundaiton Trust) contributed to study design, lead on recruitment in North London).
Mary Target (Professor of Psychoanalysis, University College London), contribute to the manual and clinical protocol of STPP, contributed to study design amd wrote papers form the study.
Barry Widmer (Project Manager, University of Cambridge) designed the database, website and managed the study.
Paul Wilkinson (University lecturer, University of Cambridge) contribute to measures, writing the BPI manual and wrote papers form the study.
Peter Fonagy (Freud Memorial Professor of Psychoanalysis, University College London) designed the study, obtained the research funding, wrote papers and wrote papers arising from the study.

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